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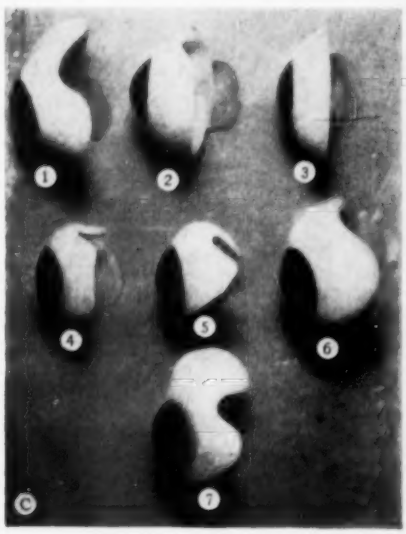

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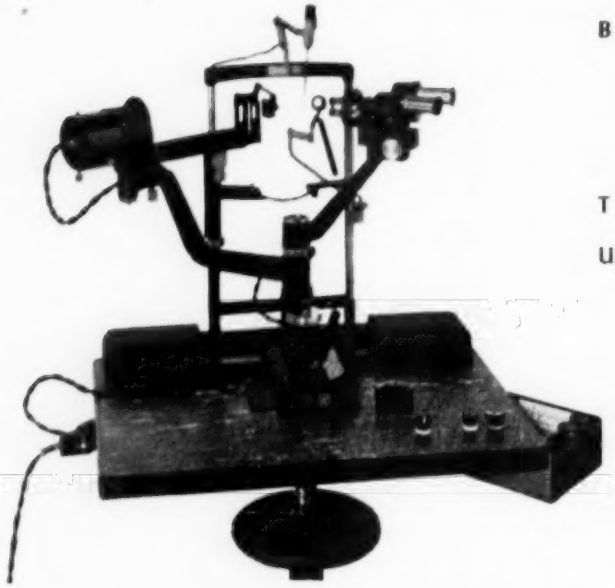

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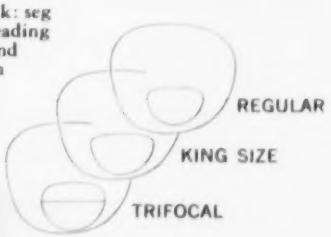

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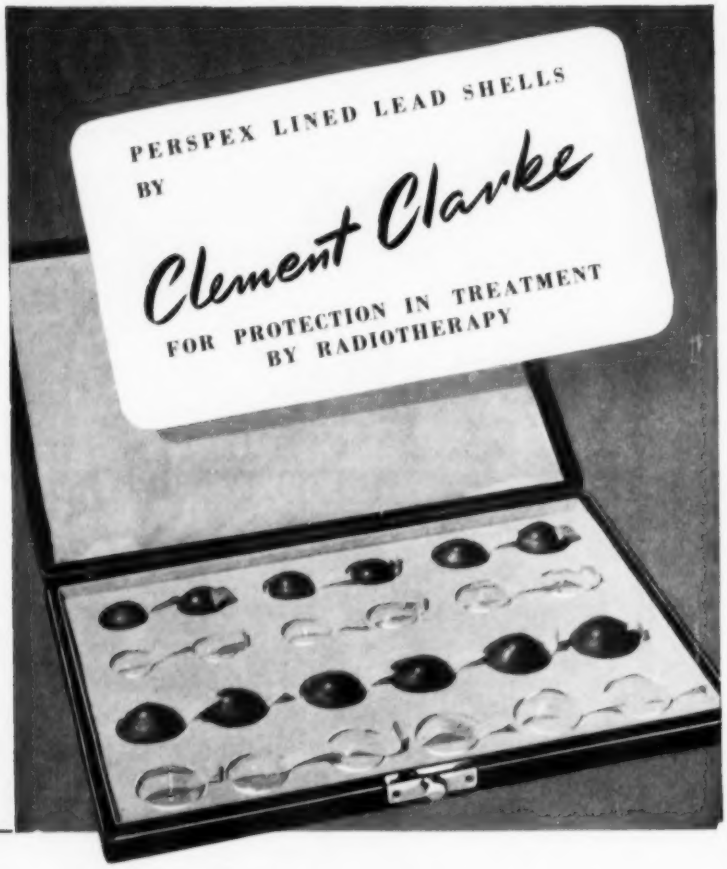

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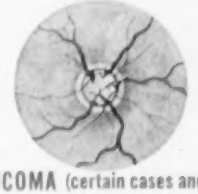

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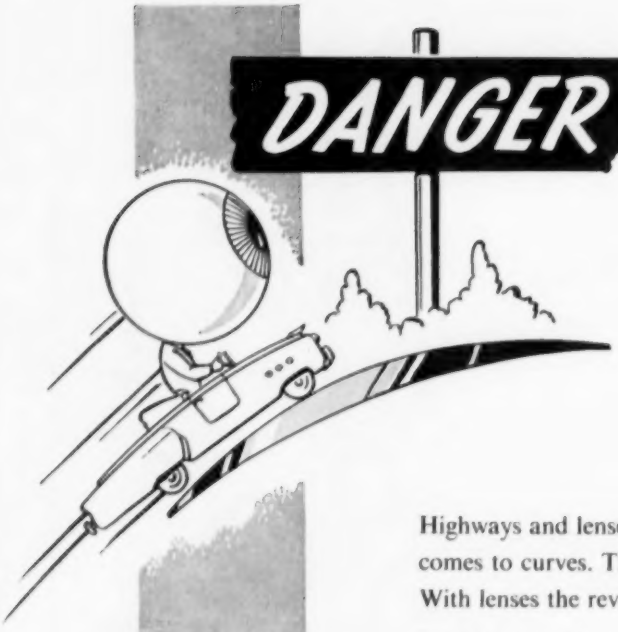

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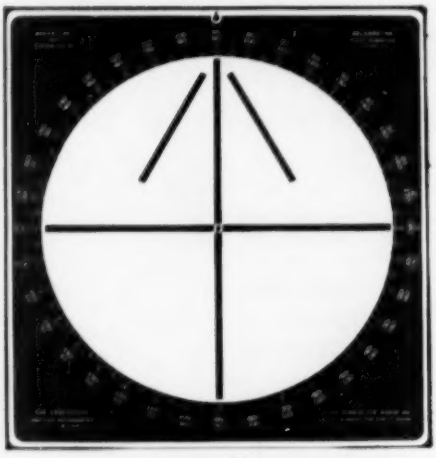

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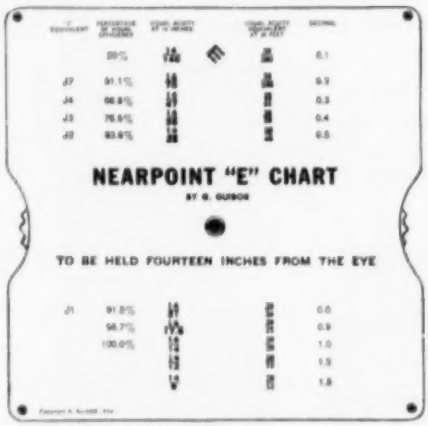

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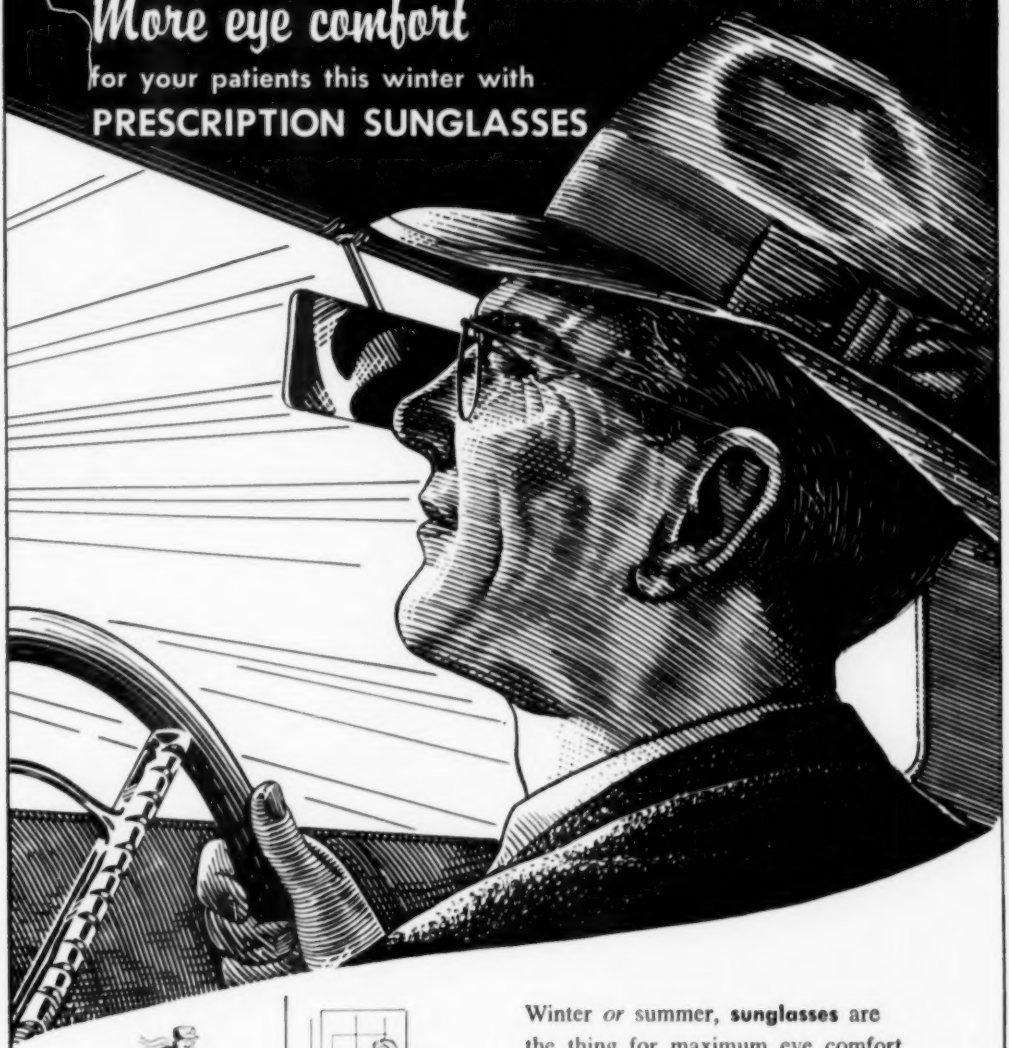

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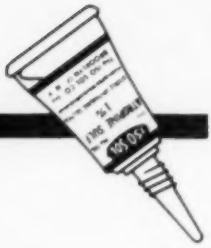

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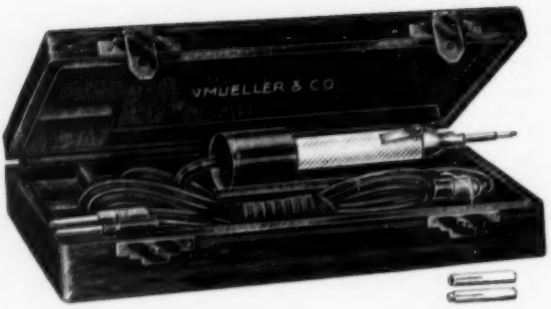

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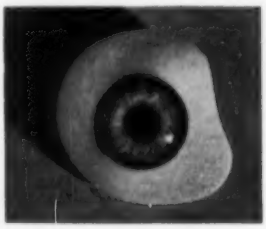

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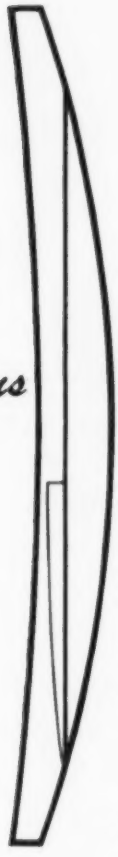

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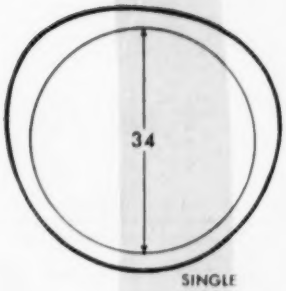

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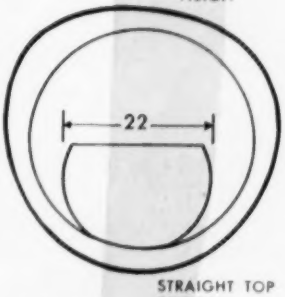

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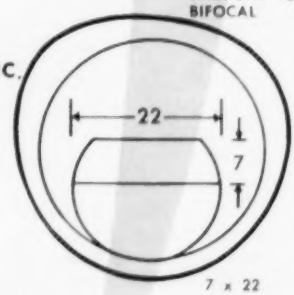

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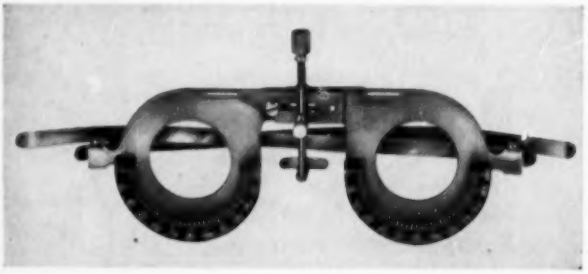

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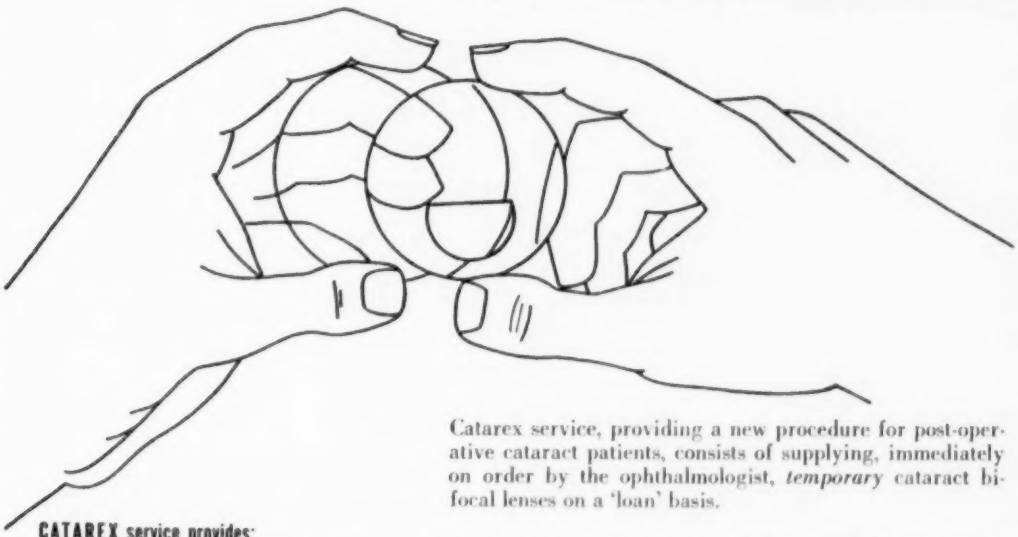

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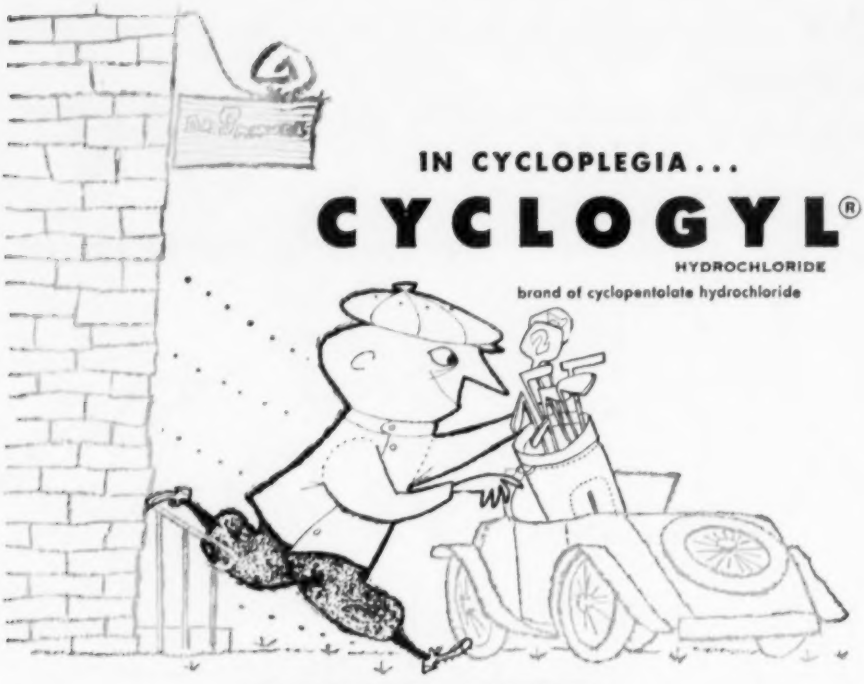

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1. Gordon, D. M., and Ehrenberg, M. H.: Am. J. Ophth. 38:831 (Dec.) 1954.

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Mortality Rates in Glaucomatous Subjects

GEORGE BENNETT, M.B., Ch.B.
Southampton, England

It is often claimed that glaucoma is not a primary ocular disease, but, rather, is a manifestation of some generalized vascular or neurovascular upset—"the sick eye in the sick body." This assertion appears to receive support from the frequent association of glaucoma with cardiovascular disease, but whether this correlation is significant remains to be proved. It is reasonable to assume, however, that if such disease had an incidence among the glaucomatous higher than in the general population, then the former should show a shorter expectation of life than average.

Few investigations to check the validity of this assertion have been undertaken. Duke-Elder [2] (1955) states that such a deviation does exist, however.

In the course of a larger investigation, I took the opportunity to put this matter to the test. This involved the follow-up of all cases of primary acute congestive and chronic simple glaucoma operated on at the Southampton Eye Hospital over some 14 years. Cases with a doubtful diagnosis, with retinal vascular complications (8 eyes), absolute glaucoma (14 eyes), and cataract obscuring the fundus (9 eyes) were excluded, as it was considered that many of these could not truly be considered cases of primary glaucoma. There remained 105 and 33 patients suffering from simple and congestive glaucoma, respectively. The age and sex distributions are shown in Table 1, the age being that obtaining when the patient was last contacted.

Received for publication Sept. 14, 1955.

TABLE 1.—*Age and Sex Distribution of Accepted Patients* *

	40-49	50-54	55-59	60-64	65-69	70-74	75-79	80-84	85-89
Chronic									
Men	3	4	9	8	12	11	9	3	2
Women	2	3	7	5	8	11	4	2	..
Totals	5	7	16	13	20	22	13	5	2
Acute									
Men	0	0	1	3	3	2	0	0	0
Women	0	2	5	3	4	5	3	1	0
Totals	0	2	6	6	7	7	3	1	0

* Age when last seen.

In addition, there was one man with chronic glaucoma aged 35 and one man with chronic glaucoma aged 31. This gives a total of 105 chronic glaucoma patients (63 men, 42 women).

There was also one man with acute glaucoma aged 36. This gives a total of 33 acute glaucoma cases (10 men, 23 women).

A number of cases (60) had defaulted in their attendances to the hospital for a period of at least six months, and nothing was known of their present condition. The sex and type distribution of these patients are given in Table 2; the age and type distributions, in Table 3.

TABLE 2.—*Sex Distribution of Defaulters*

	Men	Women	Total No. of Patients	
Acute....	1	9	10	(30% of acute glaucoma patients)
Chronic..	31	19	50	(48% of chronic glaucoma patients)

TABLE 3.—*Age Distribution of Defaulters*

	40-49	50-54	55-59	60-64	65-69	70-74	75-79	80-84	85-89
Acute	0	1	1	3	2	1	2	0	..
Chronic	2	3	4	3	11	12	8	4	2

In addition, there was one defaulter (man with chronic glaucoma), aged 35.

Table 3 includes 26 patients aged 71 or more. This group was subjected to a postal and personal inquiry so that it could be ascertained what had befallen them. The results of this investigation are given in Table 4.

Table 1 includes corrections arising from this inquiry. Of the uncirculatized 34 cases below the age of 70 years, 5 were known to be dead. We shall, therefore, be fairly safe in assuming that all the defaulters have died. The error made with this assumption will give glaucomas a higher mortality rate than their true one. With the material presented in Tables 1, 2, 3, and 4, we may build a life table for our "glaucoma population" and compare it with a corresponding table for the general population. It might be argued that this element is not a representative sample of the total glaucoma population, favoring either the mild or the severe cases. We must consider, therefore, the effect of excluding, with regard to the chronic glaucomas, (*a*) the milder cases attending hospital but not requiring surgery; (*b*) early cases, too mild to require hospital treatment before the relatively early death of the subjects, and (*c*) the cases attending hospital but rejected from this series.

The cases in (*a*) will be of all ages, not necessarily the younger groups. The number in this will be relatively large, probably greater than the patients who underwent surgery. Thus, this exclusion will load the scales heavily in favor of severity. Similarly, we could say that the (*b*) cases were scattered throughout the whole age range of glaucoma; they are rather nebulous entities altogether, and it is doubtful whether their exclusion would affect the proportions. We are left to consider whether the absence of the rejected cases would unbalance the remainder. We have already noted the chief causes of rejection, and it is clear that these causes will be allocated fairly evenly among all age groups, and thus the elimination of these cases will not upset the balance in any direction. The over-all effect of omitting (*a*), (*b*), and (*c*) will therefore be to leave as sample a group of glaucomatous eyes of severity above average.

TABLE 4.—*Results of Inquiry*

Dead	19
Alive	5
Not traceable	2
Total	26

TABLE 5.—*Age and Sex Distribution of Patients with Respect to Survival*

	Under 50	50-54	55-59	60-64	65-69	70-74	75-79	80-84	85-89
				(*a*) Surviving					
Chronic									
Men	2	2	7	6	6	5	4	1	1
Women	2	2	5	4	3	7	2	0	0
Totals	4	4	12	10	9	12	6	1	1
Acute									
Men	1	0	1	2	3	2	0	0	0
Women	0	1	4	1	2	4	2	1	0
Totals	1	1	5	3	5	6	2	1	0
				(*b*) Deceased					
Chronic									
Men	3	2	2	2	6	6	5	2	1
Women	0	1	2	1	5	4	2	2	0
Totals	3	3	4	3	11	10	7	4	1
Acute									
Men	0	0	0	1	0	0	0	0	0
Women	0	1	1	2	2	1	1	0	0
Totals	0	1	1	3	2	1	1	0	0

Table 5 gives the age and sex distribution of patients known to be still alive, with corrections from Table 4.

The acute cases total 24, including 1 aged 36. The chronic total 59, including one aged 31.

Table 5 (*b*) is Table 3 after correction by the data of Table 4, giving details of patients known or presumed to be dead. These patients total 9 with acute and 46 with chronic glaucoma, the latter including 1 aged 35. It is interesting to note that the mean age in each group is much the same, varying between 64 and 67 years (see below).

TABLE 6.—*The Chronic Glaucoma "Universe"*

Age	40	50	55	60	65	70	75	80	85	90
Alive	103	98	91	75	62	42	20	7	2	0
Dead	2	3	4	3	11	10	7	4	1	
Deaths										
Percentage of mean population	2	3	5	4	21	32	52	89	100	
Percentage expected (see Table 7)	4	4	7	11	17	28	46	73	..	

Table 6 is an extension of Table 5 (*a*) and (*b*) combined for chronic glaucoma, both sexes—the chronic glaucoma "universe."

None of the differences between the percentages in the last two lines have any significance (P always >0.05). The figures for "Percentage expected" are derived from the "Life Tables" for England and Wales given in the "Annual Abstract of Statistics 1953."[1] These Tables are based on the mortality and population returns for the years 1949-1951 and the 1951 Census. The figures given therein for men and women have been combined, so that the percentage derived is for a population with a slight excess of females (about 2%), who have a better expectation of life than males. In our series, 60% of the glaucoma simplex cases are male; so on this consideration alone we should here expect mortality rates higher than those derived from the Tables. The method of deriving the expected percentage of deaths is outlined in Table 7, in which the figures of the second column are obtained from the combined figures for males and females in the Life Tables mentioned above.

It might again be said that the death rate occurring in this specific locality might be highly selective, since the areas might contain a population differing widely in health and expectation of life from the average for the country. This is belied by the fact that the average death rate for the United Kingdom for all ages for 1953 is 11.45 per 1000 (12.2 for males, 10.7 for females); the rate for the county borough where this Eye Hospital is situated was 11.46 for 1952 and 10.86 for 1953. The mortality rates, therefore, are fairly average, as would be expected considering the site and characteristics of the town (Williams,† 1953 and 1954).

TABLE 7.—*Derivation of Expected Percentage of Deaths*

Age	No. Alive	No. Dead	No. Dying in Each Group	X*
40	18,461			
50	17,692	760	769	4.2%
55	16,950	1,511	742	4.3%
60	15,824	2,637	1,126	6.9%
65	14,160	4,301	1,664	11.1%
70	11,883	6,578	2,277	17.4%
75	8,956	9,505	2,927	28.1%
80	5,614	12,847	3,342	45.9%
85	2,610	15,851	3,004	78.5%

* X = numbers dead, expressed as a percentage of the average number of cases in the group.

Table 8 gives the acute glaucoma universe.

The expected rate is higher in every group save in the 60-65 year group. Here, the difference is not significant ($P>0.05$). From this we see there is no difference in mortality between acute or chronic glaucoma patients and the general population of the same age groups.

It is interesting to compare the two groups of glaucoma patients—those deceased and those surviving. This is done in Table 9.

† References 3 and 4.

TABLE 8.—*Acute Glaucoma Universe*

Age	40	50	55	60	65	70	75	80	85	90
Alive	32	32	30	24	18	11	4	1	0	..
Dead	0	1	1	2	2	1	1	..	..	
Deaths										
Percentage of mean population	0	3	4	14	13	13	40	..	..	
Percentage expected (see Table 7)	4	4	7	11	17	28	46	..	..	

TABLE 9.—*Comparison of Deceased and Surviving Cases, with Acute and Chronic Glaucoma*

	Deceased	Alive
Chronic glaucoma	46 patients (17 women, 29 men) 59 eyes	59 patients (25 women, 34 men) 78 eyes
Over-all prognosis	69% worse	58% worse
	(Difference not significant, $P > 0.05$)	
Average follow-up, yr. (per eye)	3.9	3.9
Mean age, yr. (when last contacted)	67	64
Acute glaucoma	9 patients (8 women, 1 man) 12 eyes	24 patients (15 women, 9 men) 32 eyes
Over-all prognosis	58% worse	62% worse
	(Difference not significant, $P > 0.05$)	
Average follow-up, yr. (per eye)	2.4	4.6
Mean age, yr. (when last contacted)	65	65

It is seen that the differences in the four parts of Table 9 are generally slight, and nowhere of significance. The two mean follow-up periods for the acute cases appear to vary quite markedly (2.4 and 4.6 years); the standard error of difference between these means, however, is 1.77, little less than the actual difference and therefore not significant.

An objection to this treatment is that the Tables consulted are valid only for one year, whereas our patients' lives are spread out over a number of years, and the total number alive at any one time varies somewhat. As mortality affects all groups equally, acute or chronic, male or female, the proportions will be similar, always provided that the death rates do not vary. We are probably justified in assuming that the rate among glaucoma patients is constant from year to year over the relatively short period in question. Examination of the relevant Tables for 1951, 1952, and 1953 show little variation in sex ratio and mortality rates for the population of England and Wales.

SUMMARY

Comparison of the relative mortality rates for a group of glaucoma simplex patients and a group of congestive glaucoma patients with those appertaining to the general population reveals no significant differences. From the ocular point of view, the patients who died resembled in every way those who survived. This seems to indicate that glaucoma patients do not suffer from any excess of the normal process of aging or of lethal vascular disease.

Clerebury, Twiggshane, Marchwood Nr.

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4. Williams, M. H. C.: Health Services of Southampton in 1953, Public Health Department, Southampton, England, 1954.

Tetracycline and Chloramphenicol Studies on Rabbit and Human Eyes

ROBERT K. ABRAHAM, M.D.
and
HERBERT H. BURNETT, M.S., Detroit

It has been observed that those antibiotics which penetrate into the spinal fluid through the so-called blood-brain barrier also penetrate into the eye through the blood-aqueous barrier. Recent reports in the literature have indicated that tetracycline penetrates into the spinal fluid in animals [1] and in humans.[2]

As no other report concerning the intraocular penetration of tetracycline has been published up to this time, we considered it of value to determine the degree of penetration of this antibiotic into the aqueous humor of rabbits and human beings. It was considered of importance to use human as well as rabbit eyes, for there have been very few reports on the intraocular penetration of antibiotics into human eyes, the supposition having been that rabbit eyes were very similar to human eyes in this respect.

Various modes of administration and dosage schedules were utilized. Also, a small number of assays were performed to determine the concentration of chloramphenicol in the aqueous humor of humans following oral and subconjunctival administration. Chloramphenicol was chosen for comparison because the penetration of this antibiotic into the aqueous humor after oral administration has been shown to be very high,* relative to the penetration of other antibiotics available in the past.

Tetracycline is an antibiotic which was recently developed, independently, by two different methods: by the catalytic hydrogenation of chlortetracycline † and by fermentation.[7] Structurally, tetracycline, chlortetracycline, and oxytetracycline ‡ are very similar and as a group are referred to as the tetracyclines or the tetracycline analogues.

Tetracycline differs from chlortetracycline in that the chlorine atom at the No.-7 position has been replaced with a hydrogen atom. Oxytetracycline differs from the aforementioned antibiotics in that an oxygen atom is substituted at the No.-7 position. The structural configuration of the tetracyclines is shown in Figure 1. As may be noted from Figure 2, chloramphenicol is not chemically related to the tetracycline analogues.

Submitted for publication Aug. 22, 1955.

From the Kresge Eye Institute, Detroit, and the Veterans Administration Hospital, Dearborn, Mich.

The trademark of Lederle Laboratories Division, American Cyanamid Company for the antibiotic tetracycline is Achromycin. The trademark of Parke, Davis & Company for the antibiotic chloramphenicol is Chloromycetin.

* References 3 and 4.

† The trademark of Lederle Laboratories Division, American Cyanamid Company, for the antibiotic chlortetracycline is Aureomycin. References 5 and 6.

‡ The trademark of Chas. Pfizer & Company, Inc., for the antibiotic oxytetracycline is Terramycin.

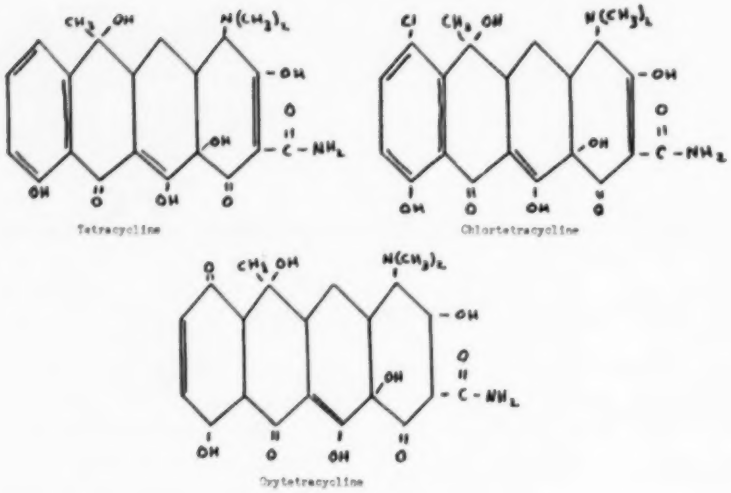

Fig. 1.—Structural configuration of tetracycline analogues.

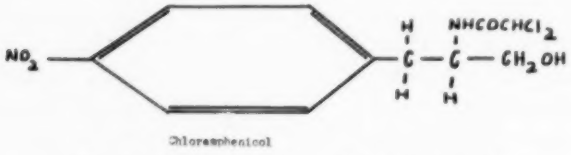

Fig. 2.—Chemical structure of chloramphenicol.

MATERIAL AND METHODS OF INVESTIGATION

Rabbit Studies

Intraperitoneal Administration. — New Zealand white rabbits were used in this study, and the tetracycline was in the form of crystalline tetracycline hydrochloride. Nine of the rabbits were given tetracycline (intravenous preparation) intraperitoneally in amounts which were equal to 30 mg. of the antibiotic per kilogram of body weight. Prior to the injection of the antibiotic a cardiac blood sample was obtained. Immediately following the injection of the antibiotic an aqueous humor sample was obtained from the right eye. A cardiac blood sample was obtained 15 minutes after the injection of the antibiotic. Cardiac blood, left eye aqueous humor (primary aqueous humor), and right eye aqueous humor (secondary aqueous humor) samples were obtained 30 minutes after injection of the antibiotic. A cardiac blood sample was obtained 45 minutes after injection. Cardiac blood, left eye aqueous humor (secondary aqueous humor), and right eye aqueous humor (tertiary aqueous humor) samples were obtained 60 minutes after the injection of the antibiotic.

The aqueous humor samples were obtained in the following manner: One per cent tetracaine (Pontocaine) hydrochloride was instilled in the cul-de-sac. The eye was proptosed, and a 27-gauge needle, to which a tuberculin syringe was attached, was passed tangentially through the cornea. Each time as much of the aqueous humor was withdrawn as was possible.

Subconjunctival Administration.—The 18 rabbit eyes in this study were divided into four groups. One eye of all the rabbits in each group received one of the following doses: (1) 5.0 mg. of tetracycline (intravenous preparation) in 0.5 ml. of sterile distilled water; (2) 5.0 mg. of tetracycline in 0.5 ml. of sterile distilled water plus 7.5 T. R. U. of hyaluronidase; (3) 5.0 mg. of tetracycline in 0.25 ml. sterile distilled water plus 0.25 ml. of epinephrine (1:1000); (4) 5.0 mg. of tetracycline of 0.25 ml. of sterile distilled water plus 0.25 ml. of epinephrine (1:1000) plus 7.5 T. R. U. of hyaluronidase.

After subconjunctival administration of these doses, aqueous humor samples were obtained at various intervals (from 15 minutes to 24 hours). Prior to obtaining each sample, the eyes were irrigated with isotonic saline and then anesthetized with 1% tetracaine hydrochloride.

Human Studies

All the human eyes used in this study were those in which cataract surgery was indicated. In most cases the aqueous humor samples were obtained the evening before the day of surgery.

The patients who received an oral or intravenous antibiotic were given meperidine (Demerol) hydrochloride (75 to 100 mg.) and phenobarbital (Luminal) sodium (grains 2 to 3 [0.12 to 0.20 gm.]) one hour before the aqueous humor samples were obtained. The patients were taken into the operating room, where sterile techniques were observed, as for intraocular surgery. A solution of 1% tetracaine hydrochloride, followed by 4% cocaine, was instilled into the cul-de-sac. A needle knife was passed tangentially through the cornea at 7 o'clock, after which a 27-gauge needle, to which a tuberculin syringe was attached, was passed through the needle-knife tract just into the anterior chamber, and the aqueous humor was withdrawn.

In those cases in which we desired secondary aqueous humor samples, a 30-minute period was allowed to elapse after withdrawal of the primary aqueous humor, and then a second sample was obtained, utilizing the original needle-knife section. In a few cases, after another 30-minute interval, a final aqueous humor sample was withdrawn. This last fluid was called tertiary aqueous humor. Each time the aqueous humor was obtained, the anterior chamber was emptied as completely as was possible.

The only untoward effect following these procedures was that of subconjunctival hemorrhage, which occurred in five patients and was due to bleeding from the conjunctival vessels at the point of fixation. These hemorrhages cleared up spontaneously. There was no noticeable effect on the cataract surgery, which took place the next morning.

Oral Administration.—Ninety-five patients were given tetracycline capsules per os on varying dose schedules. Aqueous humor samples were obtained from 14 eyes, and blood samples were withdrawn from 91 of the patients at various time intervals after the initial dose.

Sixteen patients were given chloramphenicol per os. Blood samples were taken from all these patients, and aqueous humor samples were obtained from the eyes.

Intravenous Administration.—Ten patients were given tetracycline intravenously (intravenous preparation) in amounts which were equal to 7.0 mg. of the antibiotic per kilogram of the patient's body weight. The antibiotic was dissolved in 1000 ml. of 5% dextrose in water and was administered by continuous intravenous drip, the infusion extending over a period of six hours. This was immediately followed by a second 1000 ml. of 5% dextrose in water containing the same quantity of tetracycline as the first bottle.

Blood samples were withdrawn at various time intervals. Primary aqueous humor samples were obtained from seven eyes after 11 hours of continuous infusion. The secondary aqueous humor was withdrawn 30 minutes after the primary fluid. All of these samples were obtained while the infusion was still in progress, with the exception of some of the tertiary aqueous humors and some 12-hour blood samples; in some of these cases the infusion had run out a few minutes before the sample was removed.

Local Instillation of Drops.—Using seven eyes, 1 drop of tetracycline (ophthalmic), 5.0 mg. per milliliter, was instilled in the cul-de-sacs every five minutes for six doses. Fifteen minutes after the last drop was instilled, the eyes were irrigated with isotonic saline and anesthetized with 1% tetracaine hydrochloride, and the aqueous humor samples were obtained.

Subconjunctival Administration.—Four patients in these studies were given 1.2 mg. of tetracycline (intravenous preparation) subconjunctivally, and four other patients were given 1.2 mg. of chloramphenicol (intravenous preparation) subconjunctivally. The antibiotics were dissolved in 0.5 ml. of sterile distilled water. Fifteen minutes after the injection of either antibiotic, the eyes were irrigated with sterile isotonic saline and anesthetized with 1% tetracaine hydrochloride, and then the primary aqueous humor samples were obtained. From the same eyes, 30 minutes after obtaining the primary fluid, the secondary aqueous humor was withdrawn.

Techniques

Handing of Samples.—All blood samples were heparinized to prevent clotting. Both blood and aqueous humor samples were stored in the frozen state prior to examination. The samples containing tetracycline were frozen immediately after collection and were then assayed for their antibiotic content within 48 hours thereafter. The samples containing chloramphenicol, a very stable antibiotic, were stored in the frozen state for up to two weeks before they were assayed. It has been shown § that there is no appreciable change in the activity concentrations of these antibiotics during the period of time in which our specimens were frozen.

Antibiotic Assays.—The specimens of plasma and aqueous humor containing tetracycline were assayed by a disc semimicro-agar-diffusion method,‖ using Bacillus cereus #5 (A. T. C. C. #10702) as the test organism. As a control on our method, 50 of the same plasma samples, containing tetracycline, were also assayed by a cup agar-diffusion method, using

§ Reference 8. Wheeler, L. M.: Personal communication to the authors.

‖ Dornbush, A. C., and Peloak, E. J., to be published.

the same micro-organism. Comparable results were obtained by the two methods.[9] The fluids containing chloramphenicol were assayed by a chemical (colorimetric) method.[10]

Calculations

In calculating the per cent of tetracycline which penetrated from the plasma into the aqueous humor, we utilized, in rabbits, the level of the antibiotic which was present in the plasma 15 minutes prior to the withdrawal of the aqueous humor sample. This was done in order to give some weight to the time lag in the equilibrium taking place between the level of the antibiotic in the blood and that in the aqueous humor.

In the tetracycline and chloramphenicol studies in humans, all the plasma levels used to determine the aqueous humor-plasma ratios were those obtained at the same time that the aqueous humor sample was removed, for the plasma levels were not changing markedly at about the time the aqueous humor was removed.

Results with Tetracycline

Rabbit Eyes

Intraperitoneal Administration (Table 1).—The tetracycline which was administered intraperitoneally was well absorbed into the blood stream. During the time of the experiment (one hour) the plasma level of this antibiotic did not decrease as rapidly as it would had the tetracycline been administered intravenously in one dose. This finding was of value for our determinations of the blood-aqueous ratios.

It is evident that the tetracycline penetrated into the aqueous humor of the rabbits. At 30 minutes the mean concentration of this antibiotic in the primary aqueous humor was 6.4γ/ml., while in the secondary aqueous humor the mean concentration was 12γ/ml. This represents an average of 10% of the plasma concentration of tetracycline in the primary aqueous humor and 18% in the secondary aqueous humor, an almost two-fold rise in the antibiotic level.

The eyes from which the primary and secondary fluids were obtained were exposed to the tetracycline in the blood for the same length of time. Although this latter factor did not obtain for the aqueous humor samples at 60 minutes, it is of interest to note that at this time the mean concentration of the antibiotic in the secondary aqueous humor was 12γ/ml. (21% of the plasma concentration), while at the same time the tertiary aqueous humors mean concentration was 16γ/ml. (28% of the plasma concentration).

Subconjunctival Administration (Table 2).—One cannot draw any conclusions from the small number of rabbits used other than the fact that when 5 mg. of tetracycline was injected subconjunctivally, a measurable level of this antibiotic was found in the aqueous humor. The possible effects of epinephrine and hyaluronidase on the intraocular penetration of tetracycline were not clear.

Table 1.—*Absolute Levels of Tetracycline in the Aqueous Humor and Plasma of Rabbits, Expressed in Micrograms per Milliliter.**

Administration: Intraperitoneal injection of tetracycline, 30 mg. per kilogram of body weight

	Plasma	Plasma	OS Primary Aqueous Humor	OD Secondary Aqueous Humor	Plasma	Plasma	OS Secondary Aqueous Humor	OD Tertiary Aqueous Humor
Time	15 Min.	30 Min.	30 Min.	30 Min.	45 Min.	60 Min.	60 Min.	60 Min.
Rabbit A	30	70	5.0	..	..	64	10	9
B	47	40	...	10	..	31	6	12
C	61	45	5.0	14	..	36	13	18
D	100	90	3.4	11	80	68	13	23
E	83	81	7.3	14	78	72	16	19
F	58	58	8.5	14	48	42	11	18
G	55	59	6.5	10	52	47	12	15
H	59	51	7.5	10	46	49	12	13
I	83	78	8.0	10	72	69	11	14
Mean	64	64	6.4	12	56	53	12	16

* On assay, the plasma and OD primary aqueous humor, at zero time, contained no antibiotic.

It is to be noted that while there was still some of the antibiotic present in all of the eyes tested at 6 hours, none was present in any of the eyes tested at 10 hours. Neither hyaluronidase nor epinephrine substantially prolonged the presence of tetracycline in the aqueous humor in these few eyes.

Toxicity.—In the rabbits used, even very slow intravenous injections of tetracycline in a concentration greater than 20 mg/kg. of body weight resulted in excitement, cyanosis, convulsions, and death. The same end-result was obtained if over 30 mg/kg. of body weight was given intraperitoneally.

A subconjunctival injection of 1.2, 2.5, or 5.0 mg. of tetracycline dissolved in 0.5 ml. of distilled water resulted in extreme injection and edema of the conjunctiva. A yellow discharge also appeared. All these signs of irritation disappeared three days after the initial injection when tetracycline was used alone.

When hyaluronidase was added to the fluid which was administered subconjunctivally, there was much less conjunctival injection and edema than was seen with tetracycline alone. These eyes had a normal appearance in two days.

The addition of epinephrine to the injected fluid resulted in even less initial injection of the conjunctiva than when hyaluronidase was used. However, within two to three hours after the injection the conjunctiva in these eyes (with epinephrine) appeared as congested and edematous as the eyes given tetracycline alone. These eyes recovered at the same rate as those given only tetracycline.

The addition of both hyaluronidase and epinephrine resulted in eyes which demonstrated the least initial irritative effect. After two to three hours these eyes were mildly injected, resembling the eyes given tetracycline plus hyaluronidase. They, too, had a normal appearance in two days.

TABLE 2.—*Absolute Levels of Tetracycline in the Aqueous Humor of Rabbits, Expressed in Micrograms per Milliliter*

Administration: Subconjunctival injection of 5.0 mg. of tetracycline in combination with hyaluronidase and epinephrine

Drug	Rabbit Eye	Time 15 Min.	35 Min.	1 Hr.	2 Hr.	4 Hr.	6 Hr.	10 Hr.	24 Hr.
Tetracycline*	1	2	16	16	18	16	5	..	0
	2	1	10	5	5	10	5	..	0
	3	4	5	17	..	..	..	..	..
	4	..	10	..	18	10	17	0	0
	5	4	7	10	8	7	4	0	0
Average		3	10	12	12	11	8	0	0
Tetracycline plus hyaluronidase†	6	2	2	5	5	4	5	..	0
	7	2	16	16	16	20	16	..	0
	8	4	16	16	17	..	..	..	0
	9	5	16	20	18	16	16	..	0
	10	4	15	18	11	10	6	0	0
Average		3	13	15	13	13	11	0	0
Tetracycline plus epinephrine‡	11	7	11	..	12	8	6	0	0
	12	10	14	13	10	10	..	0	0
	13	10	15	15	13	9	7	0	0
	14	8	11	12	12	10	6	..	0
Average		9	13	13	12	9	6	0	0
Tetracycline plus epinephrine plus hyaluronidase§	15	9	16	14	10	7	4	0	0
	16	13	..	15	18	..	..	..	..
	17	14	17	12	12	10	9	..	0
	18	11	13	..	10	8	7	..	0
Average		12	15	14	13	8	7	0	0

* Tetracycline 5.0 mg. in 0.5 ml. of sterile distilled water.
† Tetracycline 5.0 mg. in 0.5 ml. of sterile distilled water, plus 7.5 T.R.U. of hyaluronidase.
‡ Tetracycline 5.0 mg. in 0.25 ml. of sterile distilled water plus 0.25 ml. of epinephrine (1:1000).
§ Tetracycline 5.0 mg. in 0.25 ml. of sterile distilled water, plus 0.25 ml. of epinephrine (1:1000), plus 7.5 T.R.U. of hyaluronidase.

HUMAN EYES

Systemic Administration.—Plasma Levels: Oral administration. Table 3 demonstrates

TABLE 3.—*Average Levels of Tetracycline in the Plasma of Humans, Expressed in Micrograms per Milliliter*

Administration: (1) Oral (capsules), during a 14-hour period*
(2) Intravenous, continuous infusion for a 12-hour period†

Schedule	Dosage‡	Total Dose, Gm.	Time, in Hours								
			1	2	3	4	6	8	10	12	14
1	250 mg. q.4h.×4	1.0	..	..	..	..	..	..	..	4.9	5.0
2	500 mg. q.3h.×5	2.5	..	..	6.8	..	9.1	..	11	..	14
3	1.0 gm., then 500 mg. q.4h.×3	2.5	..	5.0	6.6	13	..	16	..	16	17
4	3.0 gm. initially; none thereafter	3.0	..	..	29	..	..	23	..	..	19
5	500 mg. q.2h.×6	3.0	..	..	..	..	..	..	..	10	9.8
6	1.0 gm., then 500 mg. q.3h.×4	3.0	..	..	..	..	..	15	..	16	13
7	500 mg. q.2h.×7	3.5	..	..	..	..	..	19	..	11	13
8	1.0 gm., then 500 mg. q.3h.×4	3.0	..	..	20	..	..	24	..	..	21
9	1.0 gm. q.h.×2, then 500 mg. q.3h.×4	4.0	7.9	..	9.3	..	18	19	13	15	16
10	1.0 gm. q.3h.×4	4.0	..	..	..	..	..	..	23	22	18
11	1.0 gm. q.h.×3, then 500 mg. q.4h.×3	4.5	..	7.9	..	12	..	14	..	16	17
12	1.5 gm. q.h.×2, then 500 mg. q.3h.×3	4.5	..	8.2	..	10	..	13	17	16	15
13	3.0 gm., then 500 mg. q.4h.×3	4.5	..	22	..	..	..	27	..	..	25
14	3.0 gm., then 1.0 gm. q.6h.×2	5.0	..	..	30	..	..	..	..	..	24
15	3.0 gm., then 1.0 gm. q.4h.×3	6.0	..	..	31	..	..	29	..	..	27
16	I.V., 7.0 mg./kg. body weight, q.6h.×2	About 1.0	8.5	..	19	..	31	45	58	57	..

* Each oral dosage schedule was administered to three to seven patients. A total of 91 patients are represented in this Table. More than 500 plasma samples were assayed.
† The intravenous infusion figures represent the average of 10 patients.
‡ The dosage schedules abbreviated in the Table are to be interpreted as follows: 1.5 gm. q.h.×2, then 500 mg. q.3h.×3 represents an initial dose of 1.5 gm. each hour for two consecutive hours, followed by 500 mg. every three hours, the latter amount to be repeated three times.

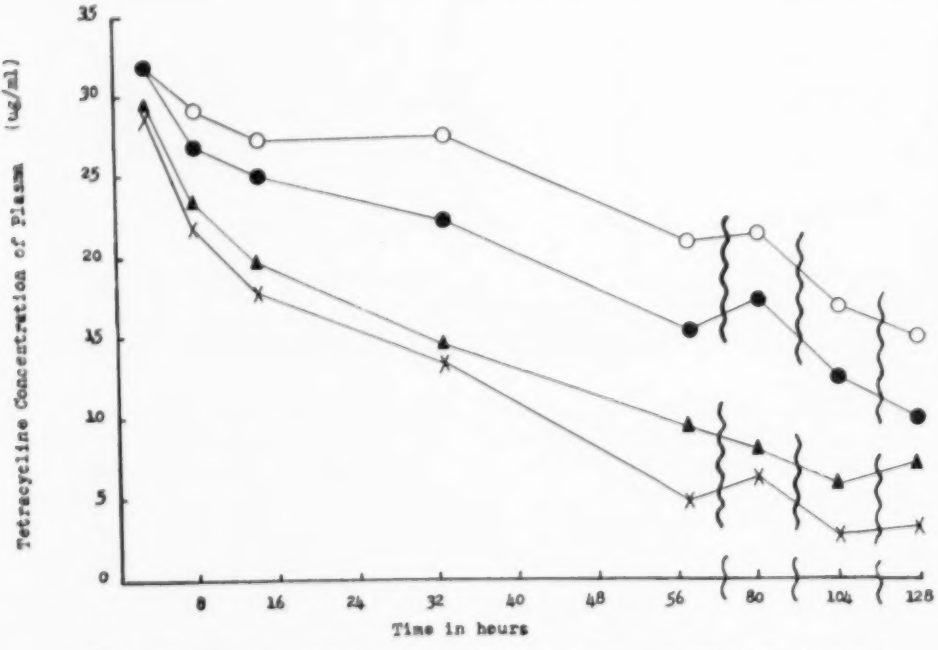

Fig. 3.—Average levels of tetracycline in the plasma of humans, expressed in micrograms per milliliter. Administration oral.

Circles indicate an initial dose of 3.0 gm., followed by 1.0 gm. every four hours. Solid circles indicate an initial dose of 3.0 gm., followed by 500 mg. every four hours. Triangles indicate an initial dose of 3.0 gm., followed by 250 mg. every four hours. Crosses indicate an initial dose of 3.0 gm., with no maintenance dose.

TABLE 4.—*Absolute Levels of Tetracycline in the Plasma of Humans, Expressed in Micrograms per Milliliter*

Administration: Continuous Intravenous Infusion*

Patient	Time, in Hours											
	1	2	3	4	5	6	7	8	9	10	11	12
W. S.	..	..	..	..	..	34	..	..	34	..	..	34
R. J.	..	..	..	..	..	50	..	..	50	..	50	50
A. P.	..	..	..	..	..	30	..	..	50	..	60	57
A. L.	..	..	..	..	..	34	..	..	34	..	..	34
I. S.	..	..	..	..	..	85	..	..	90	..	90	80
M. N.	..	..	..	..	..	96	..	..	90	..	98	96
B.	..	..	..	..	..	25	..	..	55	..	75	71
B. J.	..	..	..	..	..	25	..	..	50	..	50	50
R. H.	17	..	23	..	..	30	48	..	..	..	..	..
W. Mc.	9	..	15	..	..	18	24	..	..	..	..	..
Mean levels	..	..	..	..	..	43	..	..	57	..	..	59

* Each patient received 7.0 mg. of tetracycline per kilogram of body weight. The antibiotic was dissolved in 1000 ml. of 5% dextrose in water and administered as a continuous intravenous infusion for six hours. Another 1000 ml. of the same solution was administered for a second six hours, so that the patients received a continuous infusion for a total of 12 hours.

the plasma levels that may be obtained during a 14-hour period following the oral administration of tetracycline at various dosage schedules. Although many schedules might be used clinically, only certain ones result in a "satisfactory" plasma level at the end of 14 hours. (Our interpretation of a "satisfactory" plasma level will be discussed under "Comment." Had the maintenance doses been continued beyond 14 hours, the plasma concentration of all the patients who had received a priming dose would have been leveled off below that recorded at 14 hours. This effect may be noted in Figure 3.)

As shown in Figure 3, a priming dose of 3.0 gm. of tetracycline per os resulted, initially, in a high plasma level of this antibiotic, about 30γ/ml. Thereafter the plasma level dropped at a rate which was related to the maintenance dose of tetracycline. By about the sixth day the plasma concentrations had

TABLE 5.—*Absolute Levels of Tetracycline in the Aqueous Humor and Plasma of Humans, Expressed in Micrograms per Milliliter*

Administration: Oral and Intravenous

Patient*	Administration	Time, in Hr.†	Primary Aqueous Humor	Plasma‡	Secondary Aqueous Humor§	Plasma‡	Tertiary Aqueous Humor§	Plasma‡
I. W.	Oral	15	2.7	18	3.6	17	....	..
M. J.	Oral	14	3.1	20	4.3	19	....	..
S. R.	Oral	14	OD 4.2	18	OD 6.1	18	....	..
			OS 4.6	..	OS 5.3	..	....	..
C. B.	Oral	14	3.6	20	4.9	19	5.8	18
T. B.	Oral	14	1.9	21	2.4	21	....	..
L. M.	Oral	14	4.0	18	5.2	20	5.6	18
E. L.	Oral	14	2.1	12	2.4	..	....	..
M. Mc.	Oral	14	OD 2.3	11	OD 2.6	..	....	..
			OS 1.8	..	OS 2.1	..	....	..
T. W.	Oral	14	4.8	43	6.4	36	....	..
L. G.	Oral	3	2.0	26	4.5	24	....	..
V. B.	Oral	3	OD 2.6	25	OD 3.8	21	OD 4.8	22
			OS 2.5	..	OS 4.5	..	OS 5.1	..
A. B.	Oral	3	3.5	28	5.5	27	....	..
W. S.	I. V.	11	OD 8.6	34	OD 11	26	OD 15	28
			OS 4.4	..	OS 11	..	OS 14	..
A. P.	I. V.	11	3.8	57	5.9	50	....	..
A. L.	I. V.	11	2.4	34	4.0	41	4.4	30
I. S.	I. V.	11	6.0	90	9.0	80	13	80
M. N.	I. V.	11	7.0	98	10	96	12	90

* Dose schedules: I. W. and M. J.: 1.0 gm. q.h.×3, then 500 mg. q.4h.×3
S. R. and C.B.: 1.5 gm. q.h.×2, then 500 mg. q.3h.×3
T. B.: 1.0 gm., then 500 mg. q.3h.×4
L. M.: 1.0 gm. q.h.×2, then 500 mg. q.3h.×4
E. L.: 500 mg. q.3h.×5
M. Mc.: 500 mg. q.4h.×4
T. W.: 1.0 gm. q.h.×3, then 500 mg. q.3h.×3
L. G., V. B., and A. B.: 3.0 gm. initially, no maintenance dose
W. S., A. P., A. L., I. S., and M. N.: Continuous intravenous infusion of 7.0 mg./kg. body weight, q.6h.×2.

† Period of time elapsing between initial dose and withdrawal of the primary aqueous humor.

‡ Each specimen of plasma was obtained immediately after the withdrawal of each of the aqueous humor samples.

§ Secondary aqueous humor withdrawn 30 minutes after primary aqueous humor, and tertiary aqueous humor withdrawn 30 minutes thereafter.

TABLE 6.—*Per Cent of Tetracycline Which Penetrated into the Aqueous Humor of Humans, from the Plasma* *

Administration: Oral (capsules) and intravenous

Patient	Administration	Primary Aqueous Humor, %	Secondary Aqueous Humor, %	Tertiary Aqueous Humor, %
I. W.	Oral	15	21	..
M. J.	Oral	16	23	..
S. R.	Oral	OD 23 OS 26	OD 34 OS 29	.. ..
C. B.	Oral	18	26	32
T. B.	Oral	9	11	..
L. M.	Oral	22	26	31
E. L.	Oral	18	20	..
M. Mc.	Oral	OD 21 OS 16	OD 24 OS 19	.. ..
T. W.	Oral	11	19	..
L. G.	Oral	12	19	..
V. B.	Oral	OD 10 OS 10	OD 42 OS 42	OD 53 OS 54
A. B.	Oral	13	20	..
W. S.	I. V.	OD 25 OS 13	OD 27 OS 27	OD 50 OS 47
A. P.	I. V.	7	10	..
A. L.	I. V.	10	10	15
L. S.	I. V.	7	11	16
M. M.	I. V.	7	10	13
Aqueous humor-plasma range		7-26	10-42	13-54
Aqueous humor-plasma mean		15	22	36

* The aqueous humor level is expressed as a per cent of the plasma concentration present at the time the eye sample was obtained. See Calculation under Methods, for details.

Dosage schedule and time aqueous humor samples were obtained are the same as those shown in Table 5.

Secondary aqueous humor samples were withdrawn 30 minutes after the primary aqueous humor samples, and tertiary aqueous humor samples were withdrawn 30 minutes thereafter.

reached their base level. At this time the patients who had taken the highest maintenance dose, 1.0 gm. every four hours, had reached a plasma level of 15γ/ml., while those who had received a continuation dose of 250 mg. every four hours had an average plasma level of 7.0γ/ml.

Intravenous injection. Table 4 and Case 16 in Table 3 record the extremely high levels of tetracycline in the plasma that may be reached when the patient receives a continuous intravenous infusion. After the infusion had run for three hours, the average plasma concentration of tetracycline was 19γ/ml. By 6 hours it was 31γ/ml., and at the end of 11½ to 12 hours the concentrations averaged 59γ/ml.

Intraocular Penetration: It is shown in Table 5 that when tetracycline was administered per os or intravenously, the levels of the antibiotic which penetrated into the primary aqueous humor varied from 1.8γ/ml. to 8.6γ/ml. The concentrations in the secondary aqueous humors varied from 2.1γ/ml. to 11γ/ml., and there was from 4.4γ/ to 15γ/ml. in the tertiary aqueous humors.

The per cents of tetracycline in the plasma that penetrated into the primary, secondary, and tertiary aqueous humors are presented in Table 6. A fairly wide range of individual variations was found. The aqueous humor-plasma ratios varied from 7% to 25% in the primary aqueous humors, from 11% to 38% in the secondary aqueous humors, and from 14% to 44% in the tertiary aqueous humors.

The levels of tetracycline in the aqueous humor increased as the anterior chambers re-formed the second and third times. This is made most evident when one compares the means of the aqueous humor-plasma ratios. A mean of 15% was found for the primary, 22% for the secondary, and 36% for the tertiary aqueous humors.

Local Administration.—Topical Administration of Drops: The data in Table 7 indicate that the topical administration of drops of tetracycline in water, in the concentrations used in these patients, resulted in very little penetration of this antibiotic through the intact cornea into the aqueous humor.

Subconjunctival Injection: Subconjunctival injections of tetracycline (Table 8) in cataractous eyes with normal corneas resulted in the penetration of a small amount

TABLE 7.—*Absolute Levels of Tetracycline in the Aqueous Humors of Humans, Expressed in Micrograms per Milliliter*

Administration: One drop every four minutes for six doses of tetracycline (5.0 mg. per milliliter of distilled water)

Patient	Antibiotic Concentration*
S. R.	1.0
F. Mc.	1.7
B. B.	0
A. J.	0
M. S.	0
F. Mc.-2	0

* All samples were obtained 15 minutes after the last drop was instilled, except in the case of Patient F. Mc.-2, in which the sample was obtained 5 minutes after the last drop.

TABLE 8.—*Absolute Levels of Tetracycline in the Primary and Secondary Aqueous Humors of Humans, Expressed in Micrograms per Milliliter*

Administration: Subconjunctival injection of 1.2 mg. of tetracycline in 0.5 ml. of sterile distilled water

Patient	Primary Aqueous Humor*	Secondary Aqueous Humor†
J. Z.	2	7
F. F.	0	2
J. H.	0	0
M. D.	24‡	..

* Primary aqueous humor withdrawn 15 to 20 minutes after the subconjunctival injection.
† Secondary aqueous humor withdrawn 30 minutes after the primary aqueous humor was obtained.
‡ Aphakic blind eye with corneal scars; large quantity of xanthochromic fluid obtained.

of the antibiotic into the aqueous humor of some of the eyes. When the same solution was injected subconjunctivally into the eye of a patient with corneal scars which extended from the limbus centrally (a blind eye), the aqueous humor concentration of tetracycline was found to be extremely high.

Toxicity.—Ninety-five patients received tetracycline orally, at various dosage schedules. Five patients felt nauseous immediately after consuming the initial 3.0 gm. dose. None of these patients vomited, and all were relieved of nausea when they ate breakfast. Two patients vomited after having received tetracycline for three days. However, one of these patients was suspected of having had a myocardial infarct, although the ECG remained normal. Four patients had loose stools, but none had frank diarrhea. These patients increased their bowel movements to two or three a day.

Three of ten patients given intravenous tetracycline developed thrombi in the vein in which the infusion was given. None of these patients complained of pain during or after the infusion.

All the patients given subconjunctival tetracycline complained of a sore eye for the ensuing three days. Considerable conjunctival injection and edema resulted, plus tiny petechiae in the conjunctiva and a small quantity of yellow exudate.

No signs of irritation or symptoms other than a mild momentary stinging sensation were noted after drops of tetracycline were instilled in the cul-de-sacs of the patients tested.

RESULTS WITH CHLORAMPHENICOL IN HUMANS

Systemic (Oral) Administration.—Plasma Levels: During the first few hours following the administration of 3.0 gm. of chloramphenicol per os (Table 9), a high level of this antibiotic was found in the plasma. A

TABLE 9.—*Absolute Levels of Chloramphenicol in the Plasma of Humans, Expressed in Micrograms per Milliliter*

Administration: Oral (capsules)

Patient	Dosage Schedule*	Time, in Hours												
		1½	2	3	4	6	8	10	12	14	24	48	72	96
S. Y.	A	..	..	13	..	..	..	..	..	..	..	..	..	..
C. F.	A	41	39	..	..	..	..	..	..	..	..	..	..	..
J. B.	B	..	..	31	..	..	..	27	..	..	..	..	..	..
P. V. S.	B	..	..	35	..	..	..	27	..	..	..	..	..	..
A. P.	B	..	..	27	..	..	..	15	..	..	..	..	..	..
M. D.	B	..	..	35	..	..	..	18	..	..	..	..	..	..
A. T.	B	..	..	39	..	..	35	..	..	19	..	15	18	..
F. G.	B	..	..	40	..	..	29	..	..	21	..	16	12	13
A. R.	B	..	..	..	..	51	..	..	..	42	..	..	..	..
L. L.	B	..	..	2	..	..	..	..	11	..	22	21	7	10
E. L.	B	..	..	18	..	..	..	..	..	16	17	15	..	..
J. G.	B	..	..	..	..	38	..	..	..	33	..	..	..	..
A. J.	B	44	36	..	..	..	..	..	..	..	5	..	..	..
A. S.	C	..	..	37	..	..	..	..	..	..	16	20	19	..
E. B.	C	..	..	..	35	..	..	..	..	..	13	..	..	..
P. F.	C	..	..	..	..	..	..	..	..	21	21	21	28	..

* Dosage schedules: A: 3.0 gm. initially, none thereafter.
B: 3.0 gm., then 500 mg. q.4h.
C: 3.0 gm., then 1.0 gm. q.6h.

TABLE 10.—*Absolute Levels of Chloramphenicol in the Aqueous Humor and Plasma of Humans, Expressed in Micrograms per Milliliter*

Administration: Oral (capsules)

Patient*	Time, Hr.†	Primary Aqueous Humor	Plasma	Secondary Aqueous Humor‡	Plasma	Tertiary Aqueous Humor§	Plasma
A. R.	14	OD 22	42	..	..	..	..
		OS 20	..	..	..	..	..
L. L.	13	OD 7	11	..	..	..	..
		OS 4	..	..	..	..	..
J. G.	14	OD 26	33	..	..	..	..
		OS 20	..	..	..	..	..
E. L.	3	6	18	7	16	11	17
A. J.	1½	21	44	21	36	..	..
C. F.	1½	OD 21	41	OD 19	39	..	..
		OS 19	..	OS 21	..	..	..

* Dose schedules: A. R., L. L., and J. G.: 3.0 gm., then 500 mg. q 4h. ×3.
E. L., A. J., and C. F.: 3.0 gm. initially, none thereafter.
† Time refers to the period of time elapsing between the initial dose of chloramphenicol and the moment of withdrawal of the primary aqueous humor.
‡ Secondary aqueous humor was withdrawn 30 minutes after the primary aqueous humor.
§ Tertiary aqueous humor was withdrawn 30 minutes after the secondary aqueous humor.

TABLE 11.—*Per Cent of Chloramphenicol in the Plasma of Humans Which Penetrated into the Aqueous Humor* *

Administration: Oral (capsules)

Patient	Primary Aqueous Humor, %	Secondary Aqueous Humor, %	Tertiary Aqueous Humor, %
A. R.	52	..	..
	48	..	..
L. L.	64	..	..
	36	..	..
J. G.	79	..	..
	61	..	..
E. L.	33	44	65
A. J.	48	58	..
C. F.	51	49	..
	46	54	..
Mean	52	..	..

* Dosage schedules and time aqueous humor samples were obtained are the same as those shown on Table 10.
Secondary aqueous humor was withdrawn 30 minutes after the primary aqueous humor, and the tertiary aqueous humor was withdrawn 30 minutes thereafter.
See Calculations, as described under Methods, for derivation of the percentages.

TABLE 12.—*Absolute Levels of Chloramphenicol in the Primary and Secondary Aqueous Humors of Humans, Expressed in Micrograms per Milliliter*

Administration: Subconjunctival injection of 1.2 mg. of chloramphenicol in 0.5 ml. of sterile distilled water

Patient	Primary Aqueous Humor*	Secondary Aqueous Humor†
G. H.	8	10
J. Z.	5	..
F. F.	1	6
P. F.	3	9

* Primary aqueous humor was withdrawn 15 to 24 minutes after the subconjunctival injection.
† Secondary aqueous humor was withdrawn 30 minutes after the primary aqueous humor was obtained.

maintenance dose of 500 mg. every four hours, or 1.0 gm. every six hours, resulted in a moderately high plasma level, in most cases, even after four days of therapy.

Intraocular Penetration: An excellent concentration of chloramphenicol in the aqueous humor was usually obtained subsequent to the oral administration of this drug (Table 10). The per cent of this antibiotic which penetrated into the aqueous humor from the plasma was very high (Table 11). In these few cases a mean of 52%, or, expressed as a range, 33% to 79%, of the chloramphenicol concentration in the plasma passed into the primary aqueous humor.

Local Administration (Subconjunctival Injection).—When 1.2 mg. of chloramphenicol, dissolved in 0.5 ml. of sterile distilled water, was injected subconjunctivally, a definite level of this antibiotic was found in the aqueous humor (Table 12). In the four eyes tested, 1γ/ml. to 8γ/ml. was found in the primary aqueous humors. It is of interest to note that higher concentrations (from 6γ/ml. to 8γ/ml.) were found in the secondary aqueous humors.

Toxicity.—No untoward reactions were noted in the few cases given chloramphenicol per os.

The eyes to which chloramphenicol was administered subconjunctivally were noted, in three out of four cases, to have become

moderately injected and edematous. In one case there was a small amount of yellow exudate beneath the conjunctiva. Three of the patients complained of soreness "in" their eyes for two to three days after the injection. The fourth patient experienced no pain and had only very mild signs of irritation. All these eyes were objectively and subjectively normal by the fourth day.

COMMENT

Bacteriology of the Tetracycline Analogues and Chloramphenicol

Tetracycline is a broad-spectrum antibiotic, as are chlortetracycline, oxytetracycline and chloramphenicol.

Studies by Wright and associates [11] and English and associates [12] have demonstrated that tetracycline appears to have an antibacterial activity almost identical to that of the two previously available analogues, chlortetracycline and oxytetracycline. In both studies a wide variety of Gram-positive and Gram-negative micro-organisms were studied.

English and his associates [12] state:

> All of the gram-positive microorganisms (with the exception of two Corynebacterium species) were sensitive to tetracycline in a concentration range of 0.312 to 1.56 μg/ml. This group represented eight different genera and 22 species or strains of micro-organisms. Corynebacterium diphtheriae and xerose were the most resistant gram-positive microorganisms studied, both requiring 6.25 μg/ml. of tetracycline to produce inhibition. Comparable figures for oxytetracycline and chlortetracycline for these species were 6.25 and 3.12 μg/ml.

Tetracycline was found to be effective in a concentration range of 0.39γ/ml. to 1.56γ/ml. against nine genera which represented 13 different species of Gram-negative bacteria. It required 3.12γ/ml. of the antibiotic to inhibit Aerobacter aerogenes p, but less was required against A. aerogenes a and m. The minimum inhibiting concentration (M. I. C.) of oxytetracycline against A. aerogenes p was 3.21γ/ml. and the M. I. C. of chlortetracycline was 1.56γ/ml. An M. I. C. of 3.21γ/ml. of tetracycline was required against Neisseria gonorrhoeae and N. catarrhalis. Tetracycline showed little, if any, activity against the strain of Proteus used (M. I. C. of 100γ/ml.) and only limited activity (M. I. C. of 25γ/ml.) against the #173 strain of Pseudomonas aeroginosa used. Oxytetracycline and chlortetracycline showed the same lack of activity against the Proteus and Pseudomonas organisms used.

On the basis of the above results of English and associates, one should have a minimum concentration of tetracycline equal to 1.56γ/ml. in order to inhibit most micro-organisms in vitro. For a margin of safety in vivo (in the aqueous humor), a concentration range up to twice the 1.56γ/ml. would be considered preferable.

The field of activity of chloramphenicol is about the same as that of the tetracycline analogues. At a concentration of 3γ/ml., or sometimes even less, chloramphenicol has been shown to be effective against many Gram-negative micro-organisms and against most Gram-positive micro-organisms.

A cross resistance of various micro-organisms to all three of the tetracycline analogues has been demonstrated.[12] Therefore, if in the bacteriologic study of an infection, one found that the cultured micro-organisms was resistant to tetracycline, one would not expect chlortetracycline or oxytetracycline to be of any benefit.

Cross resistance between the tetracycline analogues and chloramphenicol is not usually found. Thus, an organism resistant to chloramphenicol would not necessarily be resistant to the tetracycline analogues.

Comparative Penetration of Tetracycline Analogues and Chloramphenicol in Rabbits

Systemic Administration. — Numerous studies ¶ have demonstrated that systemically administered chlortetracycline penetrates poorly, if at all, into the aqueous humor of rabbits. Other reports # have shown that oxytetracycline, taken per os, penetrates poorly into the aqueous humor of rabbits. It was noted that even with the administration of oxytetracycline intravenously,

¶ References 15 to 18.
# References 17 to 19.

which produced a high blood serum concentration, there occurred only very low degrees of ocular penetration.

Leopold, Nichols, and Vogel reported [2] that in rabbits, chloramphenicol penetrates well into the aqueous humor after systemic administration. Sorsby and associates [16] also reported that chloramphenicol penetrates into rabbit eyes, but to a slighter degree than that described by Leopold and associates.

Our results show that in rabbits tetracycline penetrates fairly well into the aqueous humor from the plasma (an average of 10% in the primary aqueous humor). Thus, although systemically administered tetracycline penetrates into the rabbit eye better than does chlortetracycline or oxytetracycline, it does not penetrate as well as chloramphenicol.

Local Administration.—When administered as drops, chlortetracycline * and oxytetracycline † do not penetrate through the intact corneas of rabbits. They do penetrate through the abraded corneas.‡ Chloramphenicol drops do penetrate through the intact and the abraded corneas of rabbits.[3] (We did not test the penetrability of tetracycline drops through the rabbit's cornea.)

Chlortetracycline § and oxytetracycline [19] injected subconjunctivally in rabbits result in very little penetration of these antibiotics into the aqueous humor.[15] However, chloramphenicol injected subconjunctivally into rabbits has been reported as penetrating to a fair degree into the aqueous humor.‖

When we administered tetracycline in distilled water subconjunctivally, a fair degree of penetration into the aqueous humor resulted (in rabbits). The addition of epinephrine to the injected tetracycline appeared to cause a higher initial concentration of this antibiotic in the aqueous humor, but thereafter did not elevate the antibiotic level in the eye or prolong the presence of tetracycline in the aqueous humor beyond six hours.

The effect of hyaluronidase on the penetration of tetracycline is not clear. However, further studies with hyaluronidase are indicated, employing a larger number of rabbits and using a fresh eye each time for the aqueous humor samples at the various time intervals.¶

It appears, then, that tetracycline, via the subconjunctival route, penetrates into the aqueous humor of rabbits better than its two analogues. A direct comparison of the relative penetrabilities of tetracycline and chloramphenicol in rabbits cannot be made at this time, as the amounts of the antibiotics administered were not the same in the comparable experiments.

Toxic Reactions of the Tetracycline Analogues and Chloramphenicol in Rabbits

Other research workers have administered chlortetracycline, oxytetracycline, and chloramphenicol systemically to rabbits in higher concentrations than we were able to use in our work with tetracycline. Rabbits are apparently species-sensitive to this antibiotic.# although other test animals, such as rats and mice, are able to accept very high doses without any untoward reactions.

Oxytetracycline [17] and chloramphenicol * both cause quite a bit of irritation when injected subconjunctivally.[18] Chloramphenicol does not appear to be quite as toxic.[3]

We found tetracycline to be a definite irritant when given subconjunctivally to rabbits. Epinephrine prevented the appearance of the inflammatory reaction for the first few hours after the injection, but thereafter the eyes appeared to be as inflamed as when tetracycline was given alone. Hyaluronidase, when added to the injected fluid, definitely decreased the clinical signs of irritation, and these eyes had a normal appearance one day sooner than eyes given tetracycline alone or tetracycline with epinephrine.

* References 15 and 16.
† References 17 and 19.
‡ References 16 and 17.
§ References 15 and 16.
‖ References 3 and 18.

¶ Abraham, R. K., to be published.

Dornbush, A. C.: Personal communication to the authors.

* References 15 and 16.

Comparative Penetration of Tetracycline, Chlortetracycline, and Chloramphenicol in Humans

Wood and Kipnis [2] reported that when the same quantities of each of the tetracycline analogues were administered orally to humans, a higher concentration of tetracycline than of chlortetracycline or oxytetracycline was found in the cerebrospinal fluid.

From our results, it is quite apparent that when tetracycline reaches the blood stream of humans, whether administered orally or intravenously, it penetrates quite well into the aqueous humor. The data presented (Table 6) show that in the human eyes tested, 7% to 25% (a mean of 15%) of the plasma concentration of tetracycline penetrated into the primary aqueous humor.

When we administered chloramphenicol per os to a group of patients, it was found (Table 11) that 33% to 79% (a mean of 52%) of the plasma concentration had passed into the primary aqueous humor. Leopold first reported good intraocular penetration of this antibiotic in humans following systemic administration. The eyes used in his study were enucleated for medical reasons, and then the aqueous humor was withdrawn.[4]

Saubermann [20] has reported on the penetration of chlortetracycline into human eyes which are being treated for infections. His data showed that following the oral administration of chlortetracycline very low levels of this antibiotic were found in the aqueous humor of the inflamed eyes, while in one normal eye no concentration of chlortetracycline was found at all. Following the intravenous injection of 2.0 gm. of this antibiotic, a somewhat better level than that obtained with oral administration was found in the aqueous humor (in two out of three of the inflamed eyes tested).

Our results clearly indicate that in human eyes, following systemic administration, a larger percentage of the chloramphenicol in the plasma than of the tetracycline penetrated into the aqueous humor. Both these antibiotics appear to penetrate from the plasma into the human eye better than chlortetracycline does. No study on the intraocular penetration of oxytetracycline in humans has been reported.

A comparison of the results we obtained in rabbits and in man following the systemic administration of tetracycline can be made only for the secondary aqueous humor, for in the rabbits a nearly constant level of tetracycline had by then been present for at least 45 minutes. (The blood level related to the primary aqueous humor of the rabbits had been fairly constant for less than 30 minutes.) The comparison reveals that the relative penetration in both rabbits and humans is of the same order of magnitude.

Oral and Intravenous Dose Schedules of Tetracycline

It has been noted previously that the minimum inhibiting concentration of tetracycline against most bacterial organisms in vitro is 1.56γ/ml. Our results showed that some of the human eyes tested permitted a minimum of only 7% of the plasma concentration of tetracycline to penetrate into the aqueous humor. Thus, in these patients a plasma level of 22.3γ/ml. would be required in order to achieve the minimum inhibiting concentration theoretically necessary in the aqueous humor.

One may observe from Tables 3 and 5 and Figure 3 that in order to obtain an initial level of tetracycline in the plasma greater than 22.3γ/ml. it was necessary to give a priming dose of 3.0 gm. Only a maintenance dose of 500 mg. every four hours or 1.0 gm. every four hours kept the plasma level relatively well elevated for a period of time. When 500 mg. every four hours was the maintenance dose, this period was 32 hours. Thereafter, the plasma level of tetracycline was below the minimum desirable level of 22.3γ/ml.

The schedule of 3.0 gm. of tetracycline initially, followed by 1.0 gm. every four hours, kept the plasma level at a safe height for approximately 52 hours. Thereafter, the level in the plasma, and assumedly in the aqueous humor, dropped below the desirable concentration.

On the basis of the above reasoning, we recommend two possible oral dose schedules

for tetracycline. One could administer 3.0 gm. initially, followed by 500 mg. every four hours, the entire schedule, including the initial 3.0 gm. dose, to be repeated every 24 hours. A preferable schedule would be that of 3.0 gm. initially, followed by 1.0 gm. every four hours, the entire schedule, including the initial 3.0 gm. dose, to be repeated every 48 hours. Only in this way could one be fairly sure of achieving the proper plasma and aqueous humor levels of tetracycline.

For a continuous intravenous infusion of tetracycline, we recommend 7.0 mg. of tetracycline per kilogram of body weight, dissolved in 1000 ml. of 5% dextrose in water or in saline. The infusion should run for six hours. A new bottle of fluid, containing the same amount of tetracycline, should follow the first bottle and the drip be continued another six hours, etc., so that the patient is receiving a continuous infusion around the clock.

As recorded in Tables 3, 4, and 5, this infusion would usually result, within five to six hours, in a plasma and aqueous humor level of tetracycline well above the previously noted minimum inhibiting concentration (M. I. C.). As it may require up to five to six hours to obtain the desirable plasma concentration (Table 4), one might permit the fluid to drip a bit faster during the first few hours of the infusion.

If the above volume of fluid should be contraindicated for the patient under treatment, one could then give a higher concentration of the antibiotic in a smaller volume of fluid, administering this over a longer period of time. For example, one could administer 14 mg. of tetracycline per kilogram of body weight in 1000 ml. of fluid, adjusting this to run for 12 hours, and follow it with an identical solution of tetracycline in the succeeding 12-hour periods.

Oral Dose Schedules of Chloramphenicol

Assuming a minimal penetration of 33% (Table 11), and considering that the M. I. C. of chloramphenicol, for most micro-organisms, is under 3γ/ml., a plasma level of about 9γ/ml. of this antibiotic would be required in order to achieve the desired concentration in the primary aqueous humor. The figures reported in Table 9 indicate that 500 mg. every four hours, or, better, 1.0 gm. every six hours, would result in a plasma (and, therefore, aqueous humor) level which would be entirely adequate for most cases. Should one desire to use a priming dose, one would not need as large an amount as 3.0 gm.

Factors Influencing the Blood-Aqueous Barrier

The effect of an infection, with its concomitant inflammation, and also the effect of the re-formation of the aqueous humor, upon the concentration of an antibiotic in the eye should also be considered. It is known that when an eye is inflamed, a larger percentage of the antibiotic present in the blood stream passes into the aqueous humor.† This factor would then apply not only during an infection, but also postoperatively, for there is usually some inflammatory reaction following intraocular surgery.

It is clear, from the data recorded on Tables 5 and 6, that the re-formation of the aqueous humor permitted a larger per cent of the tetracycline to pass from the plasma into the eye. The secondary aqueous humor had a higher concentration of the antibiotic than the primary fluid, and the tertiary aqueous humor had the highest concentration of all.

Either or both of the above factors increase the margin of safety in the ophthalmologist's attempt to insure an adequate concentration of tetracycline or chloramphenicol in the aqueous humor of his patients. However, one should not rely on these factors to the extent of decreasing the aforementioned dosage schedules, for, in a specific patient, one does not know with exactitude how well the antibiotic will pass into the eye. Also, the minimum inhibiting concentrations previously mentioned are figures which were arrived at in vitro. It would be desirable to have higher concentrations in vivo.

† References 21 and 22.

Local Administration of Tetracycline and Chloramphenicol in Humans

Our results demonstrate that when tetracycline is administered as drops, it penetrates poorly, if at all, through the intact corneas of humans. One would anticipate a greater degree of penetration into the aqueous humor in those eyes which have breaks in the corneal epithelium, as has been demonstrated for oxytetracycline,[17] chlortetracycline,[16] and chloramphenicol.[3]

When equal quantities of tetracycline and chloramphenicol were injected subconjunctivally into human eyes, it was found that the chloramphenicol had penetrated into the primary aqueous humor with greater consistency and in higher concentrations than had the tetracycline. Owing to the irritating qualities of tetracycline and chloramphenicol, one would not be well advised to use either of these antibiotics routinely in this manner. However, when one is fighting an intraocular infection, 1.2 mg. of tetracycline in 0.5 ml. of sterile distilled water would be the recommended dose for a subconjunctival injection. The same dose has been suggested for chloramphenicol.[3]

Toxic Reactions of the Tetracycline Analogues and Chloramphenicol in Humans

Chlortetracycline has been limited in its usage per os because of nausea, vomiting, and diarrhea, which have been reported by some investigators to occur in from 10% to 20% of the patients treated.‡

Oxytetracycline, taken by mouth, has also been shown to cause gastrointestinal reactions in patients. Various reports have placed the incidence at from 13% to 21%.§

In the few cases in which we administered chloramphenicol per os no toxic reactions were noted. Other than the effect of chloramphenicol on the hematopoietic system, practically no toxic symptoms have been described following the use of this antibiotic.‖ Many reports, however, have been published in which a depression of the hematopoietic system has been associated with the use of chloramphenicol.¶

Wright and associates[11] treated 65 patients with capsules of tetracycline with only one patient developing diarrhea (1.5%) and one a sore tongue. Putnam and associates[31] administered tetracycline capsules to 106 patients. None of these patients vomited; none had frank diarrhea; 19% had loose stools; 7.1% had pruritis ani, and 0.9% had generalized itching.

In the series of patients to whom we administered tetracycline capsules there was a very low incidence of toxic reactions. Specifically, 4% had an increased number of bowel movements (from one to three a day), but none had frank diarrhea. After taking the initial 3.0 gm. dose, 5% of the patients were slightly nauseated within a few minutes, but none vomited. These patients swallowed the tetracycline capsules a few hours before breakfast. When breakfast was consumed, the nausea disappeared in every case. After three days of therapy (at a maintenance dose of 500 mg. every four hours) only one, or possibly two, patients vomited (1%-2%).

As noted previously, a continuous intravenous infusion of tetracycline did not produce any pain. However, 3 out of 10 of the patients developed thrombi in the vessel utilized for the infusion. One would certainly not use tetracycline intravenously as a routine measure, but when one is fighting an intraocular infection, the possibility of a localized venous thrombus should not deter one from using it in this manner.

One may then conclude that, with reference to untoward reactions, the oral administration of tetracycline is to be preferred over the same mode of administration of chlortetracycline and oxytetracycline. The choice between tetracycline and chloramphenicol would depend upon one's opinion of the relationship between chloramphenicol and the blood dyscrasias attributed to its use, for both these antibiotics give rise to a very low incidence of gastrointestinal reactions.

‡ References 11 and 23.

§ References 11 and 24.

‖ References 25 to 27.

¶ References 28 to 30.

When one is attempting to decrease the incidence of nausea and vomiting that might be associated with the ingestion of antibiotics, there is a practical point to consider. It has been shown[22] that the simultaneous ingestion of antacids with chlortetracycline and oxytetracycline caused a marked decrease in their blood levels. However, simultaneous ingestion of food caused no significant alteration in their blood levels and did decrease the gastrointestinal symptoms. Thus, when one is administering tetracycline or chloramphenicol, it would be a wise precautionary measure to have the capsules given to the patient shortly after he has eaten, or, when this is not practical, the antibiotic should be taken with some milk.

When chlortetracycline, oxytetracycline, and chloramphenicol are instilled as drops in the human cul-de-sac, they cause a short-lived stinging sensation, and are otherwise well tolerated.# Tetracycline, administered as drops, was also well tolerated, for there was only a mild, momentary stinging sensation associated with its use.

Subconjunctivally, chlortetracycline caused a marked inflammatory reaction in humans. Oxytetracycline, administered in the same way, has been reported as causing very little reaction, even when used in quite high concentrations in human eyes.[19]

When chloramphenicol and tetracycline were administered subconjunctivally, in equal concentrations, to our patients, both caused marked inflammatory reactions. The irritation due to chloramphenicol was slightly less intense than that associated with the use of tetracycline.

SUMMARY

Tetracycline (Achromycin), a new broad-spectrum antibiotic which is chemically related to chlortetracycline (Aureomycin) and oxytetracycline (Terramycin), was utilized in a series of experiments designed to test the efficacy with which this antibiotic penetrates into the aqueous humor of rabbit and human eyes, following systemic and local administration. For comparative purposes, and also to test its penetrability into human eyes, chloramphenicol (Chloromycetin) was administered per os and subconjunctivally to a group of human patients.

It was noted that the bacterial spectrum of tetracycline is the same as that of chlortetracycline and oxytetracycline and is similar to that of chloramphenicol. Also, it was remarked that a bacterial cross resistance has been found among the tetracycline analogues, but none between any of them and chloramphenicol.

Observation on Rabbit Eyes.—1. Intraperitoneal tetracycline was absorbed into the blood stream and passed through the blood-aqueous barrier quite well.

2. With reference to penetrability (into the aqueous humor from the plasma), tetracycline was superior to its analogues (chlortetracycline and oxytetracycline), but inferior to chloramphenicol.

3. The concentration of tetracycline in the aqueous humor increased each time the anterior chamber was re-formed, so that the average secondary aqueous humor level was higher than the primary and the tertiary aqueous humor level was the highest of all.

4. Tetracycline, administered subconjunctivally, penetrated into the aqueous humor, but was highly irritating to the eyes at the site of the injection.

5. The addition of epinephrine to the subconjunctival tetracycline did not prolong its presence in the aqueous humor beyond that found when tetracycline was given alone (six hours). The epinephrine did decrease the inflammatory reaction to tetracycline, but only for the first two hours after the injection.

6. When the combination of tetracycline and hyaluronidase was injected subconjunctivally, there was a marked decrease in the inflammatory reaction throughout the length of the experiment, and these eyes recovered their normal appearance more quickly than when tetracycline was given alone.

Observations on Human Eyes.—Tetracycline per os resulted in good plasma levels of this antibiotic. The levels varied according to the dosage schedule followed.

References 4 and 16.

Tetracycline administered as a continuous intravenous infusion resulted in high plasma levels.

Tetracycline penetrated quite well from the plasma into the primary aqueous humor. As in rabbits, an increasingly higher percentage of the antibiotic was found in the aqueous humor each time the anterior chamber re-formed, so that the tertiary aqueous humor had the highest concentration of all.

Following the systemic administration of tetracycline (in humans), the percentage of this antibiotic which penetrated into the aqueous humor was greater than that reported from chlortetracycline (in humans).

There was a very low incidence of toxic reactions following tetracycline per os. Also, the incidence was lower than that reported for chlortetracycline and oxytetracycline.

Some of the patients who received tetracycline intravenously developed thrombi in the vein used for the infusion.

Chloramphenicol per os produced good plasma levels of this antibiotic, which then passed into the aqueous humor very well.

The aqueous humor-plasma ratios of chloramphenicol were higher than those found for tetracycline following the oral administration of these two antibiotics.

Oral dosage schedules for tetracycline and chloramphenicol are suggested. These are based upon the minimum inhibiting concentrations of these antibiotics for most microorganisms, the ability of tetracycline and chloramphenicol to penetrate into the aqueous humor of humans, and the plasma levels obtained when various oral dosage schedules are followed.

Intravenous dosage schedules for tetracycline are presented.

Tetracycline drops, in the concentration used, were well tolerated but penetrated very poorly, if at all, into the eyes tested.

Tetracycline, injected subconjunctivally, penetrated very poorly into the normal human eyes tested.

Chloramphenicol, injected subconjunctivally, resulted in fair levels of this antibiotic in the aqueous humor.

Both tetracycline and chloramphenicol were, in general, highly irritating to the eyes utilized for the subconjunctival injections. However, the chloramphenicol caused a slightly milder reaction than did the tetracycline.

Comment.—Because of the possibility of a depression of the bone marrow being associated with the use of chloramphenicol, and in spite of the fact that this drug appears to penetrate into the aqueous humor (of rabbits and humans) better than tetracycline, it is suggested that chloramphenicol be used only when one is combating an intraocular infection that is resistant to tetracycline and the other penetrating antibiotic and chemotherapeutic agents. One may then conclude that, among the broad-spectrum antibiotics, tetracycline is the drug of choice in ophthalmology when one wishes to use an antibiotic prophylactically or to combat an unidentified organism, or one which is known to be sensitive to this antibiotic.

690 Mullett St. (26).

ADDENDUM

Since the preparation of this paper, Hausler and Ormsby [33] have reported that when carbomycin (Magnamycin) hydrochloride was injected subconjunctivally, the addition of hyaluronidase to the injected fluid "reduced the inflammatory reaction and also led to increased bulbar penetration of the antibiotic." In addition, Hallett and associates [34] reported on the ocular use of tetracycline in rabbits. Their results and ours are not strictly comparable, for they administered the tetracycline intravenously in one injection, and thus the blood level was constantly changing at a fairly rapid rate. However, following the systemic administration of this antibiotic, the order of magnitude of their results and that of ours are the same. The quantities of tetracycline which they administered subconjunctivally were not the same as ours, but one may note that, with this factor in mind, the results are again, grossly the same.

Mrs. Joan L. Abraham, Miss Marilyn Hertel, and Mrs. Jane Fletcher gave technical assistance.

The American Cyanamid Company, Lederle Division, supplied the tetracycline and the culture of Bacillus cereus. Parke, Davis & Company supplied the chloramphenicol and analyzed the specimens for their chloramphenicol content, and Dr. J. E. Gajewski aided in the study.

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News and Comment

GENERAL NEWS

The Virginia Society of Ophthalmology and Otolaryngology.—The Society is sponsoring a convention cruise to Havana and Nassau from May 26 to June 2, 1956. Sailing from and returning to Norfolk, Va., the *Queen of Bermuda* will serve as the hotel for the trip. Fare for the seven days is $165 and up per person. Reservations may be made with U. S. Travel Agency, Inc., Washington, D. C.

PERSONAL NEWS

Appointment of Dr. Conrad Berens.—Dr. Conrad Berens, Life Fellow of the American Academy of Ophthalmology and Otolaryngology, and recently appointed life member of the Harvey Society, has been promoted from Associate Professor to Professor of Ophthalmology at New York University Post-Graduate Medical School. Dr. Berens is ophthalmic surgeon, pathologist, and director of research at the New York Eye and Ear Infirmary, director of ophthalmology at Midtown Hospital, and director surgeon of the Seamen's Church Institute.

Frederick Thomas Tooke Dead.—Dr. Frederick Thomas Tooke, of Montreal, Canada, died on July 20, 1955, at the age of 81. Dr. Tooke received the degree of Doctor of Medicine from McGill University in 1899 and at his death was professor emeritus of his alma mater. He had served as ophthalmologist in chief of Royal Victoria Hospital, in Montreal, and as consultant for Champlain Valley Hospital and Physicians Hospital, both of Plattsburg, N. Y. A member of the American Ophthalmological Society, he served as its president in 1939.

ANNOUNCEMENTS

A. M. A. Annual Meeting, Chicago, June 11-15, 1956.—The 105th Annual Meeting of the American Medical Association will be held in Chicago, June 11-15, 1956, with a full program of lectures, television, motion pictures, and scientific exhibits.

The lecture program for each Section is prepared by the Section Secretary, and prospective participants should communicate as soon as possible with the Secretary of the Section before which they hope to read a paper. Application blanks for space in the Scientific Exhibit are now available and may be obtained from the Section Representative to the Scientific Exhibit.

Section on Ophthalmology

Secretary: Harold G. Scheie, M.D., 313 S. 17th St., Philadelphia 3.

Exhibit Representative: Frank W. Newell, M.D., 950 E. 59th St., Chicago 37.

Additional information may be obtained from the Secretary, Council on Scientific Assembly, American Medical Association, 535 N. Dearborn St., Chicago 10.

Ocular Manifestations of Hereditary Primary Systemic Amyloidosis

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Hereditary primary systemic amyloidosis, an unusual expression of the amyloid problem, is characterized by a protean symptomatology that remarkably mimics the commonplace and the obscure. To date only four reports have appeared in the world literature describing in some detail the clinical, genetic, and pathologic constellation.* Recently three reports have appeared which emphasize the remarkable involvement of the ocular apparatus.†

As to the genesis of this universal and morbid process, much speculation has appeared in the literature in the past half-century. On the one hand, it has been held that the pathophysiology represents the end-result of an immunological reaction, and, on the other, it has been regarded as an anomaly of the connective tissue ground substance. For the greater part, these observations have been based upon, with their known limitation, fundamental animal experimental data. It has recently been suggested that secondary (parenchymatous) and primary (mesenchymal) systemic amyloidosis might represent similar and related processes. In the case of the latter, however, no demonstrable cause has been shown to exist. Recent experimental evidence suggests that, at least in part, hereditary systemic amyloidosis represents an aberrance of lipoprotein metabolism. Evidence secured in our recent study of 154 cases of primary systemic amyloidosis suggests that this unusual entity bids to replace syphilis as the great mimic. It would seem that the broad clinical expression of this disease warrants its inclusion in any differential diagnostic scheme, no matter how elemental the clinical picture or how multisystemed the pathologic process.

The eye and its adnexa may be extensively involved in this syndrome. In fact, it is theoretically foreseeable that, secondary to the predominant periarteritis, every structure and function of the eye may be deleteriously affected.

LITERATURE

A survey of the available literature reveals that of the 154 cases of hereditary primary systemic amyloidosis reported there is mention of ocular pathology in 12 cases, or 8%. The recorded signs and symptoms include (1) diplopia, (2) sudden onset of permanently reduced visual acuity, (3) photophobia and blepharospasm, (4) blurring of vision, (5) progressive visual loss, (6) anisocoria, (7) internal ophthalmoplegia, (8) bilateral exophthalmos, (9) retinal hemorrhages, (10) sluggish pupillary reflexes, (11) vitreous opacities (sheet-like), (12) patchy, whitish deposits (periarteritis) along and on the small arterioles of the retina, and (13) amyloid deposition in the walls of the central retinal artery and posterior short ciliary vessels, the lumen of the latter being virtually obliterated.

Submitted for publication Sept. 21, 1955.

University of Michigan Medical School.

This study supported in part by the Heredity Clinic, Institute of Human Biology.

* References 1 to 4.

† References 4 and 5.

PERSONAL CASES

Our observation concerns positive ocular findings in five cases of primary amyloidosis and notes on a sixth. Two of these observed cases have been previously reported by Kantarjian and DeJong [4] (1953), who very ably stressed the marked involvement of the nervous system in hereditary primary systemic amyloidosis. These cases consisted of two sisters (J. C. and M. C.) and their father (J. C.). Three other cases to be discussed comprise but a small segment of an extremely large family exhibiting a dominant mode of transmission of hereditary primary systemic amyloidosis. H. D. and L. D. are father and son, respectively, and A. D. is a first cousin of H. D.

CASE 1.—M. D. (married M. K.). This 24-year-old married woman entered the University Hospital on April 21, 1948, with complaints of blurring of vision and "dancing black spots in front of her eyes." Other complaints included weakness of the extremities, protrusion of the eyes, and persistent nausea and vomiting. The ocular symptoms had been present for at least three years. The proptosis of both eyes had been present prior to and had become exaggerated following a thyroidectomy, on March 26, 1947.

The patient's uncorrected visual acuity was 6/9—2 O. D. and 6/7.5—1 O. S.

The external examination disclosed an appreciable degree of bilateral exophthalmos. The pupils were dilated and fixed, reacting only in accommodation. The ocular motility was normal. The ophthalmoscopic examination exhibited numerous large, dense, sheet-like or film-like vitreous opacities. The optic nerve heads were moderately pale temporally. Many of the peripheral arterioles and a few venules demonstrated pinpoint to extensive plaque-like, grayish, gliotic deposits, which occasionally extended into the vitreous.

The visual field and tonographic examinations were normal O. U., with the exception of slight peripheral contraction of the visual field to a 3/330 white test object.

Exophthalmometer readings were 17.5 mm. O. U. at a base line of 101 mm. (Hertel).

The patient was again hospitalized from Aug. 8 to Nov. 19, 1948, and from Feb. 5 to April 9, 1951. During this interval she experienced progressive exacerbation of most of her symptoms. The vitreous opacities increased; the exophthalmos progressed; chemosis and lid edema appeared, and finally, exposure keratitis developed, the last necessitating an Elschnig tarsorrhaphy O. D.

The diagnosis of hereditary primary systemic amyloidosis was made on the basis of the following signs, symptoms, and laboratory proceedings: (1) psychic depression, (2) anorexia and vomiting, (3) cardiomegaly, (4) weakness of extremities, (5) loss of subcutaneous fat, (6) peripheral neuritis, (7) amenorrhea, and (8) positive evidence of amyloid in most of the small vessels of the body, found at autopsy on Aug. 13, 1952. The perineurium and epineurium of several nerves disclosed amyloid.

CASE 2.—J. C. This 23-year-old white woman, a bookkeeper, was admitted to the University Hospital on Oct. 3, 1951, with major complaints of nausea, vomiting, severe constipation, progressive weakness of the extremities, diffuse enlargement of the neck, protruding eyes, and bilateral progressive visual loss.

The patient was first seen in the Department of Ophthalmology on Aug. 12, 1952. Her history indicated that her eyes had exhibited protrusion for one year and that the pupils had been dilated for a least four months. The visual acuity had slowly decreased, especially in the right eye. The uncorrected visual acuity was 6/12—1 O. D. and 6/6 O. S. Cycloplegic retinoscopy (hydroxyamphetamine [Paredrine] and homatropine) findings were as follows:

O. D.: +2.00 sph ⁻ 0 cyl, ax 0 = 6/15

O. S.: +1.75 sph ⁻ +0.75 cyl, ax 45 = 6/6—3

The patient exhibited no accommodation in the right eye, reading Jaeger 11 type at 26 cm., and Jaeger 0 type at 14 cm. with the left eye. She could read Jaeger 0 type O. U. with a +2.50 reading add.

The external examination disclosed a fairly marked proptosis in both eyes, the exophthalmometer reading being, at a base line of 100 mm., 20.5 mm. O. D. and 21.0 mm. O. S. The ocular motility was normal. The pupils were anisocoric, the left being the larger, and both were refractory to light but not in accommodation.

The ophthalmoscopic findings consisted largely of very dense, web-like and sheet-like, hyaline vitreous opacities, some of which appeared to be attached (by foot plates) to the surface of the disc and retinal surfaces, especially at the posterior pole and intermediate region. The majority of the retinal arterioles presented dense, white or gray, glistening deposits on their surfaces, especially throughout the posterior pole and midperiphery. One ill-defined cotton-wool patch was present 4 disc diameters from the edge of the optic nerve head in the nasal retina O. S., associated with a bordering flame-shaped hemorrhage. In the extreme retinal periphery gliotic tissue was noted on the retinal surface and appeared to extend into the vitreous.

The slit-lamp, visual field, and tonographic examinations were normal O. U. One of us (H. F. F.) incorrectly diagnosed the condition in this case, suggesting the possibility of atypical Eales[1] disease which exhibited chiefly a periarteritis, and only minimally a periphlebitis.

Cycloplegic refraction findings were as follows:

O. D.: +2.00 sph ⌒ 0 cyl, ax 0 = 6/15

O. S.: +1.75 sph ⌒ +0.75 cyl ax 100 = 6/9+3

The diagnosis of hereditary primary systemic amyloidosis was made on the basis of the following signs, symptoms, and laboratory data: (1) exophthalmos, (2) horizontal nystagmus, (3) thyroid enlargement, (4) cardiomegaly, (5) gastrointestinal upsets, (6) loss of subcutaneous fat, (7) progressive weakness of extremities, (8) loss of vibratory sensation, (9) peripheral neuritis, and (10) positive family history.

Case 3.—J. C. The father of the two previously described women died in the Veterans Administration Hospital at Wood, Wis., on May 8, 1938. The ocular findings were reported to be bilateral exophthalmos and absence of pupillary response to direct light.

Autopsy findings revealed widespread primary systemic amyloidosis.

Case 4.—H. D. This 50-year-old man, a farmer, was first seen at the University Hospital Ophthalmological Clinic on June 5, 1953, with the chief complaints of "spots before the eyes," decreased visual acuity, "numbness and tingling of the hands and feet with weakness," and decreased vision over the past three to four years. Despite the fact that he was a school bus driver, his visual acuity was only 6/12+1 O. D. and 6/15±1 O. S. He could read Jaeger 7 type only poorly with either eye.

The external examination was essentially normal, as was the ocular motility.

The pupils were anisocoric, the left being larger than the right (0.5 mm.), but the pupillary reflexes were prompt and equal.

The slit-lamp examination revealed no pathology of the anterior segments. The ophthalmoscopic examination exhibited in the right eye a massive degree of dense sheets of semiopalescent, hyaline-like opacities, which waved about in the vitreous like the leaves of a marine plant and appeared to be attached here and there to the internal limiting membrane of the retina. The retinal arterioles presented patchy, disseminated, bead-like to plaque-like gray deposits on their surfaces. For the most part, these were confined to within 7 disc diameters of the optic nerve head, but an occasional deposit could be seen in the periphery of the retina. The retinal veins were similarly involved, but to a markedly slighter degree. No other gross retinal pathology could be seen, and the disc and macular area seemed unaffected. The left ophthalmoscopic picture was similar insofar as the vitreous changes were concerned, but only the faintest of retinal details could be made out. A peripheral branch of the inferior temporal arteriole presented a dense, small, white, bead-like deposit on its surface. Visual fields disclosed only a minor peripheral constriction to 2/1000 and 3/330 white test objects.

Tonometer tension was O. D. 17.3 mm. and O. S. 14.7 mm. of mercury (new Schiøtz).

The diagnosis of hereditary primary systemic amyloidosis was made on the basis of the following signs, symptoms, and laboratory findings: (1) positive gingival biopsy for amyloid; (2) cardiomegaly; (3) hypertrophic transverse carpal ligaments; (4) peripheral neuropathy; (5) 2+ globulin reaction (spinal fluid); (6) positive Congo red test; (7) intraventricular block (EKG); (8) an atypical peak, as demonstrated by free electrophoresis of the patient's serum, and (9) autopsy findings of diffuse amyloid deposition in the tongue, larynx, lungs, heart, liver, spleen, adrenals, pancreas, gastrointestinal tract, kidneys, and prostate, compatible with primary systemic amyloidosis.

Case 5.—L. D. This extremely well-developed son of H. D., age 22, was examined, at our request, on June 21, 1955. At that time he denied any significant ocular signs or symptoms.

The patient's uncorrected visual acuity was 6/9—4 O. D. and 6/9—3 O. S. The pupillary reflexes were prompt and equal in the two eyes. The pupils were round, centrally placed, and of equal diameter. The near point of accommodation was 27 cm. O. D. and 28 cm. O. S. The external, muscle motility, and slit-lamp examinations revealed no pathology in either eye.

The ophthalmoscopic examination did not disclose any disturbance in the clarity of the various media. The optic disc, macular area, and retinal periphery were normal in each eye. A grayish gliotic sheathing, of an irregular patchy distribution, of the inferior temporal arteriole, the superior and inferior nasal arterioles, and the superior temporal vein was visualized in the right eye. This sheathing varied in density from a flimsy, nebulous mist to a dense, gray, glass-bead opacity. Only a minute gliotic deposit was noted on the inferior temporal arteriole 3 disc diameters from the disc in the left eye.

Cycloplegic retinoscopy findings (hydroxyamphetamine and homatropine) were as follows:

O. D.: +1.50 sph ⌒ +1.75 cyl., ax. 90 = 6/6—2

O. S.: +1.25 sph ⌒ +1.00 cyl., ax. 80 = 6/6—2

Tonometer tension was O. D. 20.3 mm. and O. S. 20.3 mm. of mercury (new Schiøtz, new scale).

Visual fields were normal on both the perimeter and the Bjerrum screen.

The diagnosis of hereditary primary systemic amyloidosis in this patient was made, not on the

basis of signs and symptoms but, rather, on the positive findings as demonstrated by free electrophoresis (an atypical peak) and ultracentrifugation of the serum lipoproteins.

CASE 6.—A. D. This 47-year-old man (cousin of H. D.) was first examined at the University Hospital Ophthalmological Clinic on Feb. 23, 1950, at which time his major complaints were "progressive visual loss for two to three years" and "moving spots." His visual acuity uncorrected was counting fingers at 2 ft. (60 cm.) O. D. and 6/4.5—4 O. S. The pupillary reflexes were prompt and equal in the two eyes, and there was no disturbance of the size or position of the pupils. The external examination, including ocular motility, was grossly normal in both eyes. The slit-lamp examination did not reveal any pathology of the anterior segments.

The ophthalmoscopic examination presented massive, semiopalescent, dense hyaline, sheath-like vitreous opacities, so dense in the right eye that no retinal details could be elicited except for "glial proliferation from the retinal surface, noted in the extreme periphery." The left retina was normal except for a "localized white exudate on the surface of the inferior nasal arteriole."

The visual field and perimeter and Bjerrum screen determinations O. S. were normal to 3/300 and 1/1000 white test objects, respectively. There was a large central scotoma to a 8.7/1000 white test object O. D.

The tonometer tension O. U. was 23 mm. of mercury (new Schiøtz).

The patient returned May 7, 1953, stating that he had experienced a progressive, cloud-like blurring of vision. His visual acuity, uncorrected, was counting fingers at 2 ft. O. D. and a poor 6/20—1 O. S. He could read only Jaeger 11 print with the left eye. The pupils and pupillary reflexes were unchanged. The external and slit-lamp findings had likewise remained stationary except that there could be observed semiopalescent, small beads of hyaline material on the posterior surface of the right lens. The ophthalmoscopic details could not be observed in the right eye because of the massive, hyaline, sheet-like opacities of the vitreous. Grayish, bead-like deposits could be observed, through the dense, cloud-like vitreous, on the superior nasal and temporal and inferior nasal arterioles. In the extreme periphery of the retina the opacities assumed a coral-like appearance and appeared to be attached to the retinal surface.

Visual field determination was refused.

Tonometer tension was O. D. 20.3 mm. and O. S. 17.6 mm. of mercury.

Biopsy of an interdental papilla was made, but methyl violet stains were negative for amyloid.

The diagnosis of hereditary primary systemic amyloidosis was based on the following signs and symptoms and laboratory data: (1) neurologic evidence of peripheral neuropathy and hypertrophic transverse carpal ligaments, (2) extensive mucous-membrane thickening of the accessory air sinuses, (3) positive skin biopsy, (4) suggestive Congo red test, (5) atypical electrophoretic pattern, and (6) remarkable elevation of the serum lipoproteins.

COMMENT

As is true of most syndromes, considerable variation in the expression of the symptomatology of hereditary primary systemic amyloidosis is, in general, the rule. J. C., M. K., and their father, J. C., exhibited a rather constant pattern of signs and symptoms, of special ophthalmic interest being the consistent exophthalmos and the pupillary changes. A. D., H. D., and L. D., representing an unrelated Indiana family, were the only members, to date, of that family to present ocular pathology typical of primary systemic amyloidosis, the vitreous opacification and periarteritis being the significant manifestation of the syndrome in these affected persons.

It, therefore, becomes apparent that there exists considerable interfamilial variability of expression of the symptomatology depending perhaps upon the gene milieu of the affected persons. Intrafamilial similarities exist and are to be expected, with, of course, individual exceptions.

The utilization of new laboratory methods—electrophoresis of the serum and ultracentrifugation of the serum lipoproteins—has proved to be most helpful from a diagnostic stand in the study of the D. family. The typical or diagnostic electrophoretic curve presents an abnormal peak moving in the α^2-globulin area and has been termed by us the $\alpha^{2'}$ globular curve. The electrophoretic and ultracentrifugal findings in hereditary primary systemic amyloidosis serve as the basis for papers being reported elsewhere.

Both experimental methods enhance genetic evaluation of inherited disease processes. Both methods aid in detecting the not previously easily identified subclinical subject, and, furthermore, are admirably

suited to the detection and measurement of the clinically unapparent, myriad genetic variations that so aptly characterize inheritance processes.

SUMMARY

The presence of retinal periarteritis with or without associated extensive, dense, sheetlike hyaline vitreous opacities, in the absence of anterior segment inflammation, and especially in conjunction with a bizarre, unexplained widespread symtomatology, should suggest to the ophthalmologist the possibility of hereditary primary systemic amyloidosis.

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News and Comment

EDITED BY DR. W. L. BENEDICT

ANNOUNCEMENTS

Mark J. Schoenberg Memorial Lecture.—The Mark J. Schoenberg Memorial Lecture, sponsored jointly by the National Society for the Prevention of Blindness and the New York Society for Clinical Ophthalmology, will be given on Monday, Dec. 5, at 8:15 p. m., at the New York Academy of Medicine. Irving H. Leopold, M.D., chairman of the Department of Ophthalmology of the Graduate School of the University of Pennsylvania, will speak on "Recent Advances in the Medical Treatment of Glaucoma."

This annual lecture is a memorial to the late Mark J. Schoenberg, M.D., who founded the New York Society for Clinical Ophthalmology and who also was the first chairman of the National Society's Committee on Glaucoma.

SOCIETY NEWS

Oxford Ophthalmological Congress.—The next meeting of the Oxford Ophthalmological Congress will take place in Oxford at the School of Physiology, S. Park Rd., on Monday, Tuesday, and Wednesday, July 2, 3, and 4, 1956.

Mr. J. W. Tudor Thomas, of Cardiff, has been elected Master, and Mr. O. M. Duthie, of Manchester, Deputy Master.

Dr. Jonas S. Friedenwald, of Baltimore, has accepted the invitation to deliver the Doyne Memorial Lecture at this meeting and follows in the steps of his father, Dr. Harry Friedenwald, who was the Doyne Lecturer in 1930.

Any American colleagues who might wish to attend the meeting should get in touch with the honorary secretary, I. C. Fraser, 21 Dogpole, Shrewsbury, England.

Los Angeles Society of Ophthalmology and Otolaryngology.—A dinner meeting was held on Sept. 1, 1955, at the Los Angeles County Medical Association Building, in Los Angeles. James H. Allen, M.D., Professor of Ophthalmology, Tulane University of Louisiana School of Medicine, was the guest lecturer. His subject was "Principles of Treatment of Infectious Diseases of the Lids, Conjunctiva, and Cornea."

Adrenosem (Carbazochrome) in Primary Glaucoma and Diabetic Retinopathy

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Adrenochrome is one of the principal oxidation products of epinephrine and has no significant pressor action. It has been studied in Europe since 1937 and in America since 1951 for its action in control of bleeding from capillaries and venules. Its role seems independent of the chemistry of coagulation, the vitamin K-prothrombin mechanism, and the function of heparin or the usual anticoagulants. It is alleged to reduce capillary permeability and to increase capillary resistance,* a statement echoing data in regard to rutin several years ago. Both natural and synthetic adrenochrome are markedly unstable and insoluble. Evolution of the adrenochrome monosemicarbazone sodium salicylate complex has overcome these chemical difficulties. This product is synthetically prepared in America under the trade name Adrenosem and the generic name of carbazochrome.

PREVIOUS REPORT

In an uncontrolled, preliminary report of 69 private patients with bleeding problems, Sherber [4] found gratifying clinical courses following carbazochrome administration in all but 3 cases. These three were post-tonsillectomy (two) and postprostatectomy (one) patients receiving only single injections of carbazochrome in perhaps inadequate dosage. Seven patients had hemorrhagic complications of hypertension (Grade 3 and 4 hypertensive retinopathy, subarachnoid hemorrhage, epistaxis) but showed normal bleeding and clotting time prior to carbazochrome therapy. An increased Gothlin index of capillary fragility in another patient was not influenced by carbazochrome.

Our previous study [5] of capillary mechanisms in primary glaucoma showed no relation between capillary fragility or morphology and primary glaucoma. Capillary filtration or permeability, as indicated by cutaneous lymph flow did, however, show wider scatter and a statistically significant greater average flow in 50 primary glaucoma patients than in 50 control patients. This increase was most marked in patients with optic nerve head changes. Capillary counts in the forearm showed the same distribution in the glaucoma and in the control group, but the increase in number of patent loops after intradermal histamine injection was less in the glaucoma patients. This study suggested, in similarity to the problem of epidemic dropsy, in which glaucoma is one feature of a generalized disease due to capillary defects, that increased permeability and decreased mobilization of capillaries may be responsible for a segment of cases which currently are lumped together in the complex of primary glaucoma.

PURPOSES OF PRESENT STUDY

The first purpose of the present study is to correlate capillary filtration (permeability) and mobilization (histamine response) with clinical findings in white patients with (A) primary glaucoma and

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From the University of Louisville School of Medicine, Section on Ophthalmology.

These studies were supported in part by a grant from the S. E. Massengill Co., Bristol, Tenn.

* References 1 to 3.

(B) diabetic retinopathy. A third group (C) of nondiabetic and nonglaucomatous patients, under similar selection criteria serves as a control.

The second purpose is to evaluate effects of chronic medication with carbazochrome and identical-appearing placebo tablets in alternate patients of each group.

PROCEDURE

Selection of Patients.—1. Studies were restricted to white patients free of sun tan, because even small amounts of skin pigmentation interfere with visualization of skin capillaries.

2. Glaucoma patients (A) were nondiabetics selected from the glaucoma clinic of the University of Louisville or from private practice and had detailed ophthalmic records of at least six months' duration. Diabetic cases (B), similarly, were nonglaucoma patients from the diabetic clinic or private practice and had complete medical records. Control cases (C) were glaucoma- and diabetes-free outpatients of the eye clinic under management for nonvascular ophthalmic problems.

3. Patients were screened and excluded for hypertension, cardiac disease, kidney impairment, peripheral vascular disease, and hemorrhagic disorders on the basis of history, previous records, sphygmomanometer readings, and routine laboratory studies.

4. In each glaucoma case diagnosis was made on the basis of increased intraocular tension, field defects, consistent clinical findings, and absence of known factors responsible for secondary glaucoma.

Ophthalmic Studies.—1. All patients were examined for visual acuity without glasses, with glasses, and with glasses and pinhole discs.

2. Glaucoma patients (A) had electronic tonography of computation of the coefficient of aqueous outflow and were classified gonioscopically as to the type of filtration angle. Optic nerve heads were graded as to color, size of optic cup, and amount of undermining.

3. Diabetic retinopathy patients (B) were classified under five stages according to Wagener,[6] and photographs of the posterior pole were made in many cases.

Capillary Function Studies.—1. Cutaneous lymph flow as a direct index of capillary filtration was measured by intradermal injection of approximately 0.04 cc. of a dark colloidal dye. Sterile patent blue† was injected in the midvolar skin of the forearm according to the McMaster technique.[7] One minute was allowed for the force of injection to be absorbed, and then a base tracing was made of the dye area. Fifteen minutes later a second tracing was made, and the distance the dye had traveled in the longest streamer was measured in a straight line from the periphery of the base tracing. A spread of 19 mm. or more suggests pathologically increased filtration. The dye is nontoxic, and all discoloration disappears in 18 to 48 hours.

2. Capillary counts were made by tabulating the number of loops in a 2 mm. square area on the forearm marked out by rubber stamp. This area would just fit within the field of the capillary microscope. Counts below 6 or 7 suggest spasm or sclerosis. Counts up to 40 or 50 occasionally are seen in apparently healthy subjects, especially young adults. After the first tabulation, the total number of loops in the same area was determined following a few pinpricks (without drawing blood) through a drop of 1:1000 histamine solution immediately distal to the stamped area. In such an histamine flare, the capillary number normally doubles, or at least increases by 6 or 7. Considerable increase after histamine suggests capillarospasm; failure of a lower initial count to increase indicates capillary sclerosis.[8]

Incidental Data.—Room temperature was recorded at the time of each examination and varied between 78 and 89 F, with usual values in the upper 80's. Wet- and dry-bulb humidity calculations at each examination varied between 31% and 69%, with usual values in the upper 40's.

Program.—Paired patients were selected in each of the groups A, B, and C and, without our knowledge of the type of medication, placed on medication with 1 mg. tablets of carbazochrome (Adrenosem Lot No. E 315421 H) ‡ or an identical-appearing placebo tablet (Lot No. 084379) ‡ five times a day (8 and 11 a. m. and 1, 3, 5, and 8 p. m.). No change was made in the usual routine of diabetes or glaucoma control.

A. Glaucoma patients were reexamined at one- and two-week intervals. Tonograms were repeated at each examination.

B. Diabetic retinopathy patients were reexamined at 3-, 6-, 9-, and 12-week intervals, with repeated fundus evaluations at each examination.

C. Control patients were reexamined once only—at an interval of seven days.

All capillary function tests and measurements of visual acuity were repeated at each examination.

† Supplied by Dr. John Q. Griffith Jr., 2518 W. Harold St., Philadelphia 32.

‡ Supplied by Mr. P. E. Carman, Research Department, the S. E. Massengill Company, Bristol, Tenn.

RESULTS

From the screening of about 300 diabetes and glaucoma patients, 43 were obtained for initial study and institution of medication. Of this group, adequate follow-up was secured in 11 cases of primary glaucoma, 8 cases of diabetic retinopathy, and 14 control cases.

A. Primary Glaucoma Patients.—Eleven patients, all with open-angle type; age range, 28 to 78, with an average of 63.5 years. Five received carbazochrome, and 6 received placebo tablets.

1. Intraocular Tensions: These remained stable, at pretreatment levels of 17 to 44.5 mm. Hg (Schiøtz), without significant alteration in any patient.

2. Coefficient of Facility of Aqueous Outflow (cubic millimeters per minute per millimeter Hg; normal about 0.11 to 0.44 cu. mm., with an average value of 0.22 cu. mm/min/mm. Hg): Sixty electronic tonograms were made on 20 eyes of the 11 patients, with a range of 0.04 to 0.40 cu. mm/min/mm. Hg in coefficient value. Two patients had distinctly low coefficients, and on the high end of the distribution only two patients reached average normal values; the remaining seven cases showed low normal coefficients. Only one eye (Case 9) showed a significant change in coefficient value, and this was an increase from 0.19 to 0.35 cu. mm/min/mm. Hg while on placebo medication; it was also associated with a drop in lymphatic flow of from 15 to 3 mm.

3. Lymphatic Flow: Thirty-three measurements were made, with values ranging from 3 to 20 mm. The average initial flow was 10 mm., which is identical with the average value obtained in the control series of our first study[8] and only 1 mm. lower than the average for the control series (C) in this study. Flow values remained stable throughout experimentation in all but four cases: Two of these showed drops of 12 and 8 mm. while on placebo medication, and one showed an increase of 12 mm. on placebo medication; one patient showed a drop of 7 mm. while on carbazochrome therapy. Only one patient had a flow value (19 mm.) above 18 mm., which has been considered the upper limit of average normal lymphatic flow.

4. Capillary Loop Counts: These varied in the expected range of 1 to 50 per 4 sq. mm. of skin area and in all cases showed adequate response to histamine. There was an apparent trend for higher capillary counts (20-40) to be associated with lower coefficient values (0.05 to 0.10 cu. mm/min/mm. Hg), and the highest coefficient values (0.20 to 0.40 cu. mm/min/mm. Hg) were associated with the lowest capillary counts (6 and under). There was no significant change in counts in either treatment group.

5. Euphoria was observed in some patients late in the study, but mood levels were not systematically recorded throughout the experiment. One man and one woman in this group, particularly, showed euphoria, but both were on placebo medication.

B. Diabetic Retinopathy Patients.—Initial and one follow-up study were obtained on 13 patients and four consecutive examinations were completed in 8 patients; the age range was 35 to 73, with average of 54.6 years; 6 received carbazochrome, and 7 received placebo tablets.

1. Diabetic retinopathy Grade 1 to 3 was present in each case, and no case of retinitis proliferans was included. No significant change was noted in any of the 25 observable fundi during the 3 to 12 weeks of medication.

2. Lymphatic Flow: Forty-three measurements were made, with values ranging from 1 to 15 mm. The average initial flow was 8 mm. (in 14 cases), which is slightly better than the average initial flow value of 11 mm. in the 16 control cases (C). Flow values remained stable in all but four cases: Two of these showed decreases of 6 and 7 mm., respectively, and two showed increases of 4 and 7 mm., respectively, without relation to the type of medication.

3. Capillary Loop Counts: These varied in the expected range of 1 to 45, and failed

to show an appreciable increase after histamine in four cases. These four patients were receiving placebo medication and had had diabetes 8 to 21 years on moderately large (20 to 80 units) doses of insulin daily. No patient showed significant variation in capillary count on any reexamination.

4. Visual improvement of significant degree was noted in one eye only (Case 33), and this was the less good eye of a patient with moderate diabetes, aged 72, with improvement from 5/200 to 20/200+. The patient was receiving carbazochrome.

C. Nondiabetic, Nonglaucomatous Control Patients.—An initial and one follow-up examination were obtained in 14 patients in the age range of 31 to 61, with an average of 45.4 years. Nine received carbazochrome, and five received placebo tablets.

1. Lymphatic Flow: Thirty-one measurements were made, with values ranging from 2 to 18 mm. The average initial flow was 11 mm. (in 16 patients). Flow values remained stable in seven patients. Of the five patients receiving placebo medication, two showed decreases in flow by approximately 50%, and one showed a similar increase in flow. Of the nine patients receiving carbazochrome, four showed 40% to 60% decrease in flow and none showed increases. In general, those cases with higher initial rates (13 to 18 mm.) showed the greatest decreases in flow, whereas those with initially low values (2 to 13 mm.) showed insignificant changes, regardless of the drug administered.

2. Capillary Loop Counts: These varied within the expected range of 2 to 20, and in all but one case (Case 26, age 46) showed adequate increases of nearly 100% following histamine. There was no change in the pre- and post-treatment counts or histamine responses in any patient on carbazochrome therapy except two (Cases 19 and 20), who had significantly lower counts on their second study. These two patients, incidentally, had higher initial lymph flows of 18 and 15 mm., with drops to 12 and 6 mm., respectively.

SUMMARY AND CONCLUSIONS

Forty-three primary glaucoma, diabetic retinopathy, and control patients, carefully screened from the white population of eye patients in this area, have been studied for correlation of capillary function with their ocular disease. Alternate members of these groups have also been treated with carbazochrome (Adrenosem) or identical-appearing placebo tablets.

The control patients showed an average initial lymph flow of 11 mm. in 15 minutes, which is essentially the same as the value in our previously reported control group. A few subjects showed moderate changes in flow value under medication, but there was no consistent alteration in either the patients receiving carbazochrome or those receiving placebo tablets. Capillary loop counts varied within the expected normal range and showed no significant reduction following medication except in two patients with low initial counts in the carbazochrome-treated group.

All of the 11 primary glaucoma patients had the open-angle type and had low coefficients of facility of aqueous outflow. Average lymphatic flow and capillary loop counts were not influenced by medication. There was a trend for higher (20-30) capillary loop counts to be associated with lower coefficients of facility of aqueous outflow (0.05-0.10 cu. mm/min/mm. Hg) and vice versa. Intraocular tension was not influenced by medication.

The diabetic retinopathy patients all had Grade 1 to 3 fundus changes, and none showed alterations on carbazochrome or placebo medication. Average lymph flow values (8 mm.) were slightly lower than in the control group (11 mm.) but generally remained stable and reflected no changes with medication. Capillary loop counts were essentially the same as in the control group and were also uninfluenced by the drugs used.

Under the conditions of this study, carbazochrome could not be demonstrated to have

significant effect on intraocular tension, the coefficient of facility of aqueous outflow, diabetic retinopathy, cutaneous lymph flow, capillary counts, or capillary mobilization.

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Heyburn Building (2) (Dr. Keeney).

Bilateral Central Retinal Artery Occlusion

Occurrence in a Patient with Cortisone-Treated Systemic Lupus Erythematosus, Sickle Cell Trait, and Active Pulmonary Tuberculosis

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Occlusion of a central artery of the retina is a not uncommon occurrence. It is usually associated with arteriosclerosis, or less often with embolization from endocarditis, but may also be seen with syphilis, periarteritis nodosa, polycythemia vera, thromboangiitis obliterans, and temporal arteritis. A much rarer condition, however, is the occlusion of both central retinal arteries. The following is a case report of a Negro woman with proved systemic lupus erythematosus, sickle cell trait, and active pulmonary tuberculosis who suffered complete occlusion of the left central retinal artery, followed 13 days later by complete occlusion of the right central artery. This patient was treated with cortisone.

REPORT OF A CASE

A 36-year-old Negro housewife was admitted to the University Division Chest Service of Kings County Hospital on May 21, 1954, because of malaise, fever, and productive cough. In 1951 the patient began to have mild temperature elevation, cervical adenopathy, and progressive swelling, tenderness, and limitation of motion of the fingers of her right hand and both wrists, elbows, knees, and temporomandibular joints. In addition, at about the same time she had noticed swelling around the eyes and a skin rash over the forehead, cheeks, and bridge of the nose. On a previous hospital admission, in March, 1953, hepatomegaly and supraclavicular, axillary, and cervical adenopathy were found. Hyperglobulinemia, a B. U. N. between 20 and 30 mg. per 100 cc., 1+ proteinuria, microscopic hematuria, and a positive Mazzini test were also noted. Biopsy tissue from a papule on the forehead showed round-cell infiltration of the skin appendages and vessels on histologic examination; supraclavicular lymph node biopsy showed reticuloendothelial hyperplasia, and a L. E. cell preparation was markedly positive. A chest roentgenogram did not show any cardiac or pulmonary pathology. Cortisone therapy was begun on April 16, 1953, after the diagnosis of systemic lupus erythematosus had been established. The patient responded well to the drug. She became afebrile; her joint swelling and adenopathy subsided considerably, and she felt much better. She was treated with cortisone, 25 mg. daily, and was observed at monthly intervals while on the Home Care Service. She continued to do well until April, 1954, when she developed fever, malaise, sore throat, a cough productive of large amounts of yellowish sputum, and left pleuritic pain. These symptoms failed to respond to treatment with penicillin, and the patient was readmitted to the hospital.

The patient's past history is significant only in that at the age of 12 she developed bilateral ulcerations around the lower third of the tibia, which followed trauma and were slow in healing. These ulcerations recurred in 1949, after her third pregnancy, and have necessitated several hospital admissions in the past five years. A biopsy of one of these areas in August, 1950, showed "chronic inflammatory change with giant cells, and thickened blood vessels within which the red cells did not appear sickled." She had never been told of any anemia and prior to 1950 had never complained of arthralgia. In April, 1952, she was operated upon for a fibrous band across the right ureter, which had caused right hydronephrosis. The family history was unimportant.

Physical examination on admission revealed a well-developed, well-nourished Negro woman, who was coughing and complaining of left pleuritic pain. Her temperature was 103 F; her pulse rate was 124 per minute and regular; her respiratory rate was 28 per minute, and her blood pressure was 115 systolic and 80 diastolic. There was a diffuse

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maculopapular rash present over the skin of her forehead, face, and both arms. Her pupils were round, regular, and equal and reacted to light and in accommodation; examination of her fundi was negative. Her pharynx was moderately injected, and a few small, discrete posterior cervical lymph nodes were present. There was no tracheal deviation, and the thyroid was not enlarged. Examination of her chest showed fullness, bronchial breathing, and medium-moist rales in the left first anterior interspace in the midclavicular line. Her heart was not enlarged, nor were there any thrills, rubs, or murmurs. Her liver could be percussed 1 in. (2.5 cm.) below the right costal margin in the midclavicular line, but no other masses or organs could be distinguished. There was a well-healed scar in the right flank. On pelvic and rectal examination a moderate cystocele was noted. There were swellings of her wrist and proximal interphalangeal joints bilaterally. Healed ulcerations were present over the medial aspect of the lower third of both tibiae, and there was a small, draining ulcer just above the right medial malleolus. Her neurological examination was normal.

The results of the laboratory tests were as follows: Urinalysis: The specific gravity was 1.012; 1+ proteinuria was found; there was no glucose or acetone. An occasional red blood cell was noted on microscopic examination. She had 11.6 gm. of hemoglobin per 100 cc., 3,790,000 red blood cells per cubic millimeter, a hematocrit reading of 35%, and a leucocyte count of 14,000, with 76% polymorphonuclears, 16% band forms, and 8% lymphocytes. No abnormal red blood cell forms were seen on stained smear, and the platelets appeared adequate. The erythrocyte sedimentation rate was 48 mm. in one hour (Wintrobe), and the reticulocyte count was 1.6%. The sickle cell preparation, using sodium metabisulfite as the reducing agent, was positive. Filter-paper electrophoresis of the patient's hemoglobin demonstrated approximately 70% normal and 30% sickle cell hemoglobin. This finding was consistent with the sickle cell trait. The Mazzini test was positive, but both the Kolmer and the cardiolipin (V. D. R. L.) test were negative. An L. E. cell preparation was markedly positive. Blood chemical levels were as follows: urea nitrogen, 18-30 mg. per 100 cc.; total protein, 8.4 gm. per 100 cc.; albumin, 3 gm. per 100 cc.; globulin, 5.4 gm. per 100 cc.; calcium, 8.3 mg. per 100 cc.; phosphorus, 4.0 mg. per 100 cc.; alkaline phosphatase, 1.6 Bodansky units per 100 cc.; sodium 138 mEq. per liter; potassium, 4.2 mEq. per liter; chlorides, 101 mEq. per liter; carbon dioxide-combining power, 62 vol. %; cephalin flocculation, 2+; cholesterol, 140 mg. per 100 cc.; bilirubin (total), 1.1 mg. per 100 cc. The Bromsulphalein test showed 0% retention after 45 minutes. The phenosulfonphthalein test revealed 63% excretion after two hours. The electrocardiogram showed regular sinus tachycardia and left axis deviation. Blood cultures on three occasions were sterile. Tubercle bacilli were demonstrated both on smear and in culture of the patient's sputum. A roentgenogram of the chest on admission revealed a large cavity with a fluid level in the apical posterior segment of the left upper lobe, with left hilar infiltrations and involvement of the superior segment of the left lober lobe. The roentgenograms of both wrists and hands showed periarticular swelling of the soft tissue about the proximal interphalangeal joints and osteoporosis at the ends of the phalanges and wrist bones. The roentgenogram studies of the skull, ankles, and feet were negative. On arterial (brachial) puncture the sample contained 44.50 vol.% of carbon dioxide, an oxygen content of 13.11 vol.%, and an oxygen capacity of 14.41 vol.%. The arterial oxygen saturation was calculated to be 91.0%. The clotting times (Lee-White) were 10, 12 and 17 minutes; the bleeding time was 3 minutes. The prothrombin time was 14.2 seconds, with a control of 14.6 seconds. The recalcification time was 120 seconds, the same value as the control. Clot retraction was good in one hour.

The patient was treated initially with streptomycin, 1.0 gm. daily; isoniazid, 300 mg. daily, para-aminosalicyclic acid (PAS), 12 gm. daily, and procaine penicillin G, 1,000,000 units intramuscularly twice daily, the last because of the possibility of a concomitant bacterial infection. On July 3, 1954, the patient had a severe allergic reaction to the paraaminosalicylic acid. This disappeared when that drug was discontinued. The patient continued to have intermittent high temperatures and exacerbations of her arthritis, both of which were felt to be manifestations of systemic lupus erythematosus. Because the patient's chest findings, both clinically and roentgenographically, were improving considerably on antimicrobial therapy, cortisone was continued, in an attempt to control the lupus erythematosus.

On Nov. 11, 1954, while still having a temperature of 103-104 F, the patient awoke with blindness and pain in the left eye. Examination disclosed vision of 20/30+1 in the right eye and only light perception with projection in the left eye. Tension (Schiøtz) was 16 mm. in the right eye and 21 mm. in the left eye. There was no abnormality in the right fundus. The left optic disc was well visualized and sharp. The arterial tree was almost completely obliterated, the arteries and arterioles showing severe attenuation, and segmentation was present in those vessels that could be seen. The veins appeared intact, although somewhat diminished in caliber, and no pulsations of the veins at the disc were noted. The entire retina was blanched and presented a yellowish-white color. The macula

appeared brownish-red and stood out prominently in the center of the blanched retina, presenting a picture of the so-called "cherry-red" macula. A diagnosis of left central retinal artery occlusion was made, and the patient was given pyridil carbinol (Roniacol) tartrate, 50 mg. orally every four hours, amyl nitrite inhalations, and nicotinic acid, 50 mg. every eight hours. Observations at frequent intervals over a period of one week failed to show any change in the picture of the fundus of the left eye.

On Nov. 24, 1954, the patient awoke and noticed that vision in the right eye was gone. Examination at that time disclosed that there was present only light perception with projection in the right eye and light perception with faulty perception in the left eye. Tension (Schiøtz) was 18 mm. in the right eye and 14 mm. in the left eye. The right fundus presented the picture of a "cherry-red" macula within a blanched retina. The arterial tree was markedly attenuated, and there were no venous pulsations noted at the disc. The left fundus showed no change from the picture previously described. In addition to continuation of the vasodilating therapy, a right anterior chamber paracentesis was performed, with local and topical anesthesia. On Dec. 30, 1954, the patient was able to perceive hand movement at 1 ft. with the right eye and was able to count fingers at 2 ft. with the left eye. Ophthalmoscopic examination at that time revealed little change except that there appeared to be better color in the left retina, and the macula was not as outstanding in appearance. On Feb. 21, 1955, both discs had a somewhat atrophic appearance, while both maculae appeared granular, the right more so than the left. The retina of both eyes appeared to have taken on a better color, although there was still present a marked attenuation of the arterial tree. At this time, a soft white fluffy exudate was noted about 1½-2 disc diameters below the right disc, giving the appearance of a typical retinal cytoid body.

On cortisone therapy, the patient continued to run a febrile course, though her arthritis subsided. About Nov. 15, 1954, the cortisone was tapered off and then discontinued, and corticotropin gel, 25 units intramuscularly daily, was administered. This change in therapy was followed by a gradual remission of the fever. Under streptomycin and isoniazid (Rimifon) therapy, the large cavity in the apical posterior segment of the left upper lobe had shrunk considerably. Of the last six gastric cultures, only one has shown growth of tubercle bacilli. Small subcutaneous nodules in the region of both olecranon processes have appeared and then regressed after about two weeks. Histological examination of one of these nodules revealed several areas of fibrinoid necrosis. L. E. cell preparations have remained consistently positive.

At present the patient is being maintained on corticotropin gel, 25 units daily; streptomycin, 1 gm. twice a week; isoniazid, 100 mg. three times a day; KCl, 2 gm. a day, and a low-salt diet.

COMMENT

Theoretically, it is possible for the bilateral central artery occlusion in this case to have resulted from any one of the three diseases proved to be present in the patient: sickle cell trait, pulmonary tuberculosis, or systemic lupus erythematosus. In addition, the cortisone given in treatment of the last disease may have contributed to the clinical picture. All four factors may give rise to vascular occlusion phenomena, and, in the absence of histological material from the retinal arteries, one must speculate as to which of the four produced the lesions.

It has long been thought that the sickle cell trait was of very little clinical significance.[1] Of great recent interest, however, has been the discovery that patients with the trait may develop clinical manifestations referable to sickling. Smith and Conley[2] report 12 patients with proved sickle cell trait, none of whom had ever previously been suspected of having sicklemia, who when flying at high altitudes (10,000-15,000 ft.) developed splenic infarctions. Studies utilizing filter electrophoresis have demonstrated that the erythrocytes of patients with the sickle cell trait contain from 24%-45% sickle cell hemoglobin, the rest being normal hemoglobin. Only 1 of the 12 patients described by Smith and Conley was shown to have slightly more sickle cell than normal hemoglobin in his erythrocytes. The mechanism postulated in these cases was a reduction of oxygen tension, leading to intravascular sickling of erythrocytes, with a resultant occlusion of small vessels. Henderson and Thornell,[3] in low-pressure-chamber studies of Negro aviation cadets having the sickle cell trait, were unable to find intravascular sickling or increased erythrocyte hemolyses at pressures simulating 15,000 ft., where the arterial oxygen saturation was 75%. Findlay and associates[4] found only 0.8%, 1.2%, and 5.0% sickling in three

Negroes with the sickle cell trait who were kept at 15,000 ft. for 15 minutes. Several cases* have been reported of vascular thrombi consisting of sickled red blood cells in patients who were not anemic and who gave little or no past history of symptoms usually connected with sickle cell anemia. Most of these case reports did not include electrophoretic analysis of the patient's hemoglobin, and therefore it is impossible to state whether the sickle cell trait or some other variant, such as sickle-hemoglobin C disease, was the etiologic factor. We have observed a patient who had thrombosis of a pulmonary artery, causing infarction of a lobe of his lung, due to sickle cell disease.

Severe anoxemia in our case may have led to the intravascular sickling of the patient's erythrocytes. However, there is no clinical or laboratory evidence that any severe degree of hypoxia was present to cause this phenomenon. The second condition under which sickling in vivo might conceivably occur would be the presence of an abnormal amount of sickle cell hemoglobin, which, in its reduced state, has been shown to have a considerably higher viscosity than normal hemoglobin.[8] Analysis of the patient's hemoglobin by filter-paper electrophoresis showed a distribution of approximately 70% normal and only 30% sickle cell hemoglobin. We must conclude, therefore, that we are without good clinical or laboratory evidence on which to relate the bilateral central retinal artery occlusion to the patient's sickle cell trait.

The retina is very rarely involved in tuberculosis as a primary affection.[9] Apart from the lesions seen in miliary tuberculosis, there may be extension from an adjacent ocular structure, such as the ciliary body, choroid, or optic nerve. Thrombus formation in the pulmonary vein may be a source of systemic arterial emboli,[10] and, although never reported, could conceivably involve the retinal arteries. Tuberculous retinitis is very rare, and is characterized by the appearance of numerous yellowish-white exudative lesions or, in some instances, by a larger area of exudation, accompanied by congestion and dilatation of the vessels and occasional hemorrhages into the vitreous. Von Hippel,[11] in 1935, reported a case of tuberculosis of the choroid in which short stretches of two retinal arterioles were closed by intimal proliferation, with epithelioid and giant cells present. In our patient, the adjacent eye structures gave no evidence of tuberculous involvement, nor was there evidence of widespread pulmonary or miliary dissemination, such as was reported in the cases† in which systemic arterial embolic phenomena occurred. Because of this, it is difficult to see how the patient's pulmonary tuberculosis was directly related to the bilateral central retinal artery occlusion.

The frequency of retinal involvement in systemic lupus erythematosus varies from 20%[14] to 51%.‡ Retinal changes may be secondary to severe renal involvement and hypertension or atypical verrucous endocarditis with system arterial embolic pathology. In addition, primary retinal lesions may be representative of the widespread changes in connective tissue matrix found in disseminated lupus. Pathologically,[15] the vascular system, particularly the arterioles, have been shown to undergo a progression of changes, beginning with edema and fibrinoid degeneration within the subendothelial layer. Further deposition of rings of fibrinoid may lead to encroachment upon the lumen, with seminated lupus. Pathologically,[16] the vascular occlusion. Rarely one may find, in addition, either a fulminating necrosis of the muscular lamellae or thrombus formation within the lumen. Koch and McGuire[16] observed progressive obliteration of many small retinal vessels in a patient ill with systemic lupus erythematosus. Retinal cytoid bodies are of considerable diagnostic significance and have been observed in almost 25% of a large group of patients.[17] They are thought to represent ischemic ganglioform degenera-

* References 5 to 7.

† References 12 and 13.

‡ Bader, R., and Bader, M.: Personal Communication to the authors.

tion of the retinal nerve fibers [18] and, in the absence of arteriosclerosis associated with hypertensive renal disease or diabetes, severe anemia, increased intracranial pressure, or septicemia, are considered extremely suggestive of systemic lupus erythematosus.[19]

To our knowledge, bilateral central artery occlusion has never been included among the ocular manifestations described in systemic lupus erythematosus.§ It does not seem unlikely that the retinal arteries could be involved by a pathological process similar to that described for other vessels in this disease. The fact that the vascular occlusions in the retina occurred during the time when the patient's systemic lupus was active, together with the consistently positive L. E. cell preparations and the histological demonstration of fibrinoid necrosis in a subcutaneous nodule, adds further credence to the speculation. The subsequent appearance of a retinal cytoid body, in the absence of other conditions in which it may be observed, is collateral evidence for the entire retinal pathology being caused by systemic lupus erythematosus. It has been reported ‖ that cortisone and corticotropin may induce a state of hypercoagulability of the blood, leading to thromboembolic complications. Patients with underlying vascular disease appear more prone to develop these complications. The increased coagulability which may be demonstrated in certain of these patients by a decreased venous clotting time is also thought to be directly influenced by the dose of corticotropin or cortisone. In this case, however, the coagulation studies performed failed to reveal any acceleration of the clotting mechanism, and it is difficult to attribute the central retinal artery occlusions, even in part, to a state of hypercoagulability caused by cortisone or corticotropin administration. Although sickle cell trait and the skin ulcers probably were a manifestation of sickle cell disease, we have no evidence that there was any severe anoxemia, sufficient to produce intravascular sickling and subsequent thrombosis. We think it highly unlikely that the patient's pulmonary tuberculosis was the cause of the retinal vascular occlusions.

Although the sickle cell trait was reported to influence pulmonary tuberculosis adversely,[25] a more recent study [26] has demonstrated it to have no influence upon the degree or clinical course of the disease.

Of great interest in this patient's course is the finding that the active pulmonary tuberculosis with cavitation, which was produced initially by the deleterious effects of cortisone in causing a healed tuberculous lesion to become reactivated and to spread, demonstrated healing and arrest of the process under antituberculous therapy despite the continuance of the steroid therapy. Experimental studies in animals and reports of the association of reactivation with serious spread and dissemination of tuberculosis in humans are numerous.¶ It has been reported as occurring in steroid therapy for lupus erythematosus.# There are certain diseases, of which this patient is an example, in which cortisone and antituberculous therapy have to be combined. The coexistent diseases require both therapeutic agents, and it is our experience that diseases such as lupus erythematosus, leukemia, Addison's disease, rheumatoid arthritis, and coexisting tuberculosis do well when therapy with the two drugs is carefully controlled. Likewise, antituberculous therapy is advocated as a prophylactic measure for any patient requiring prolonged cortisone or corticotropin therapy. We employ it, for example, in patients who have sarcoid who receive cortisone therapy. We have never seen these patients develop pulmonary tuberculosis. A combined form of therapy of this nature has been advocated by others, with equally good results.*

Our patient has her lupus erythematosus well controlled, with regression and inactivation of her pulmonary tuberculosis, with

§ References 20 to 22.

‖ References 23 and 24.

¶ References 27 to 29. Wells, M., and Wells, H. A.: Unpublished observations.

References 31 and 32.

* References 40 and 41.

cavity closure and sputum conversion. Thus, when they are needed for over-all therapy, cortisone and corticotropin do not exert a deleterious effect when they are carefully combined with antimicrobial therapy for tuberculosis.

SUMMARY

1. A case is reported of bilateral central artery occlusion occurring in a patient with proved systemic lupus erythematosus, sickle cell trait, and pulmonary tuberculosis who was treated with cortisone.

2. The vascular and retinal lesions in these conditions are discussed.

3. It is concluded that the bilateral central retinal artery occlusion seen in our patient was most likely due to the systemic lupus erythematosus present.

Dr. R. Janet Watson and Dr. Herbert Lichtman gave us the use of their laboratory facilities, and Mrs. Ellen Eschenbrenner and Mr. Vernon Delgado performed the electrophoretic and coagulation studies.

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News and Comment

GENERAL NEWS

Postgraduate Program in Ocular Pathology.—A postgraduate program entitled "Ocular Pathology," under the chairmanship of Dr. James H. Allen, Professor of Ophthalmology, will be presented Dec. 5-9, 1955, through the Division of Graduate Medicine of Tulane University of Louisiana School of Medicine.

In addition to formal lectures and demonstrations, four hours of each day will be devoted to the study of microscopic sections.

Registration must be limited to 12, and registrants will be expected to bring their own microscopes and substage lamps. Inquiries should be addressed to the Director, Division of Graduate Medicine, 1430 Tulane Ave., New Orleans 12.

Section on Ophthalmology, American Medical Association: Call for Papers.—The 1956 meeting of the Section on Ophthalmology will be held in Chicago, June 11-15, 1956, simultaneously with that of the Association for Research in Ophthalmology.

Anyone wishing to present a paper before the Section is urged to communicate as soon as possible with Dr. Harold G. Scheie, 313 S. 17th St., Philadelphia, 3. A title and an abstract of 50 to 150 words must be in his hands by Jan 1, 1956. Anyone wishing to present a paper before the Association for Research in Ophthalmology should contact the secretary, Dr. Lorand V. Johnson, 10515 Carnegie Ave., Cleveland 6, as soon as possible.

Members are reminded that their contributions to the Knapp Fund are now due and payable to Dr. Parker Heath, Sullivan, Maine. A $10.00 contribution entitles you to a volume of the 1955 *Transactions of the Section*. Contributions in excess of $10.00 are invited.

The Use of Absorbable Gelatin Film (Gelfilm) in Glaucoma Filtration Surgery

JOSEPH LAVAL, M.D., New York

The success of fistulizing operations for the relief of hypertension in glaucoma depends in large measure upon the creation of a filtering area in the subconjunctival spaces. While it can be argued that the filtration factor is not the entire answer to the problem, as maintained, for instance, in the neurohumoral theory, it is certainly one of the most potent reasons for the prevalence of these procedures in this country.

In order to secure permanent filtration from the anterior chamber to the immediate subconjunctival spaces, many substances working upon the principle of the seton operation have been employed, such as threads, gold drains, and horsehair, and quite recently Qadeer [1] has employed acrylic plates made of the same material as that used for the Ridley implants. Most of these substances have been discarded after trial and failure because they were irritating to the eye and, as a result, frequently increased the amount of fibrous tissue proliferation and caused rapid sealing of the fistulizing channel. In this country the most commonly used substance is the iris itself, in the iris inclusion techniques.

To help obtain good filtration, we previously suggested the oral use of cortisone, both pre- and postoperatively, and provided experimental evidence in favor of this form of therapy.[2] There are times, however, when it is inadvisable to administer cortisone or hydrocortisone over prolonged periods. Moreover, evidence has accumulated * which shows that eventually fibrosis does take place despite administration of cortisone, the cortisone effect lasting only a matter of months. Accordingly, we have searched for other methods that would not be contraindicated in any patient and that would be longer lasting.

A material which we believe fulfills these requirements is absorbable gelatin film (Gelfilm). Gelfilm is a sterile, nonantigenic, absorbable film, approximately 0.075 mm. in thickness, made from pig gelatin. While dry it feels and behaves like Cellophane of approximate thickness; when wet it assumes a soft, rubbery consistency, which allows it to be fitted to any body surface. Its rate of absorption in the body varies with the tissue in which it is implanted, being anywhere from one to six months.

Using Gelfilm in dogs to replace dura, Scheuerman and associates [3] found that in animals killed 15 to 28 days postoperatively the intact Gelfilm was found encased in an envelope of connective tissue, the outer layer adherent to temporal muscle and the inner overlying the brain, from which it was separated by a clear area without any adhesions. In 70-day-old wounds they found only isolated fragments of Gelfilm. Amazingly enough, the fibrous tissue envelope, where the Gelfilm had been, maintained a separation between the outer and the inner layer, the latter layer being continuous with intact dura. Microscopically the cellular reaction was minimal, consisting of a few round cells, an occasional polymorphonuclear cell, but no giant cells. This lack of cellular reaction applied to all animals regardless of when they were killed. Weisel and associates [4] obtained similar results when working with the Gelfilm as a substitute for human pleura.

Submitted for publication July 1, 1955.

*Laval, J., and Coles, R.: Unpublished data.

Thus, adhesions between dura and brain, and pleura and lung, were apparently prevented by Gelfilm. Weinmann and Correll,[5] working on Gelfilm implants in muscles, showed that the site where the absorbed Gelfilm had been was similar microscopically to a lesion created by merely separating the muscle fibers.

Here, then, was a material which we felt would be ideally suited to ocular surgery in view of its nonantigenicity, its lack of undue inflammatory reaction, and its slow absorbability, leaving a clear space beneath it. We felt that it would be especially suited to those cases in which the filtering bleb becomes extremely large. This condition is usually due to adhesions about the bleb which prevent the subconjunctival dissipation and absorption of the aqueous from the anterior chamber. As a result, backflow ensues, with hypertension and failure of the procedure. Very frequently, merely cutting into the bleb and spreading the scissors will cause the tension to decrease as the aqueous finds new subconjunctival channels for filtration. We felt that Gelfilm could be used to prevent these adhesions and to provide a larger subconjunctival drainage area, and that it could also be employed as a seton overlying the iris as it emerges from the anterior chamber in the iridencleisis operation. We conceived the idea of placing a strip of Gelfilm between the conjunctiva and the prolapsed iris over the episcleral tissues to prevent adhesions of the conjunctiva to the episclera. Accordingly, we undertook the following animal experiments in order to test the validity of this concept.

ANIMAL EXPERIMENTS

Material and Technique

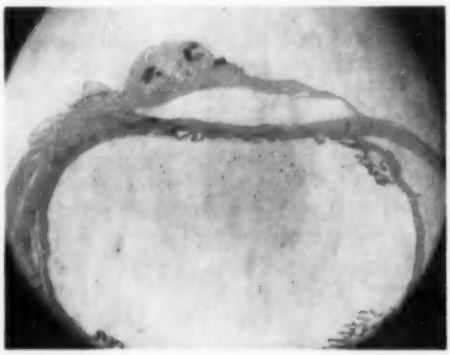
A total of six rabbits (12 eyes), between the ages of 3 and 6 months, were employed. All rabbits received topical anesthesia with 2% tetracaine hydrochloride and intravenous pentobarbital (Nembutal), 6 mg. per kilogram of body weight. Each animal received 300,000 units of procaine penicillin G intramuscularly.

Two techniques were employed: Procedure 1 consisted of dissecting a large conjunctival flap in the equatorial region and placing a strip of Gelfilm measuring 4×20 mm. on the episclera. The conjunctiva was then sutured tightly in place. Procedure 2 consisted of making a large conjunctival flap beneath the nictitating membrane, dissecting it down to the sclera and clearing to the limbus. At this point a keratome section was made into the anterior chamber. A strip of Gelfilm measuring 3×15 mm. was then introduced into the anterior chamber in such a manner that one-half was within the anterior chamber and one-half was lying on the sclera. The conjunctiva was then tightly closed.

Results

In all the rabbit eyes examined, regardless of the duration of the Gelfilm implantation, the constant finding was the total absence of any inflammatory reaction. Whether the substance was placed in the anterior chamber or subconjunctivally, the most that could be found at the sites of implantation was an occasional round cell and here and there a fibroblast. The Gelfilm itself, as absorbed, broke up into small fragments, which disappeared without leaving any trace. No foreign body reaction was found on any of the slides prepared. Another unusual aspect of these slides was the presence of large clear, empty spaces where the Gelfilm had been present. The laxness of the subconjunctival tissues resulted in these spaces not becoming obliterated. They were not lined by fibrous tissue. However, these spaces were also present when the Gelfilm was used as a seton into the anterior chamber. Figure 1 shows the eye of a rabbit killed at the end of eight weeks in which the Gelfilm had been placed on the episcleral

Figure 1



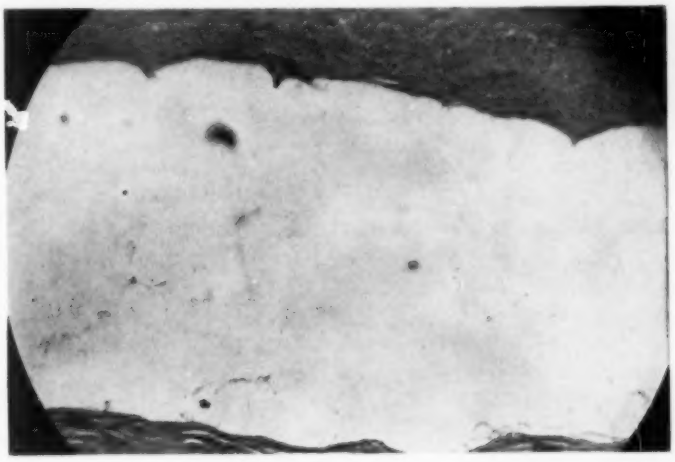


Figure 2

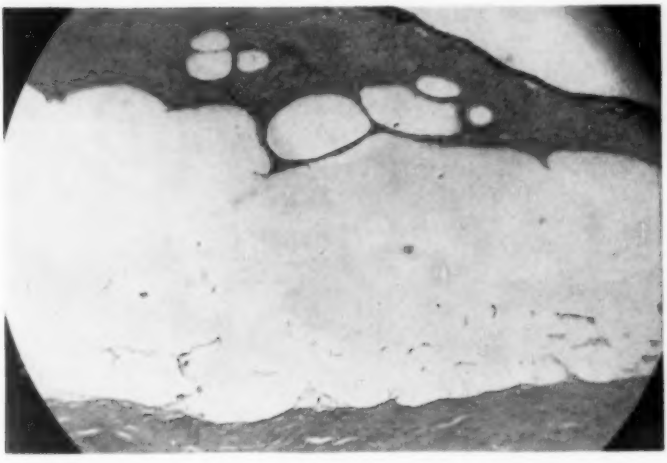
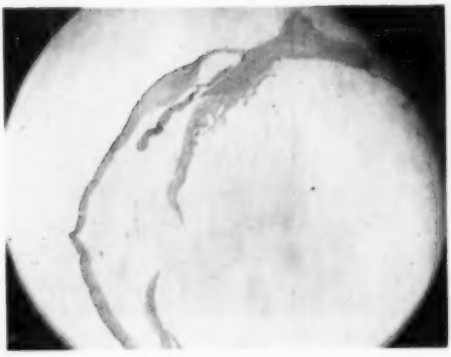


Figure 3

Figure 4



tissue. Figures 2 and 3 are both enlargements of areas from the picture. The large clear areas and the absence of inflammatory reaction, with and without the presence of the Gelfilm, are amply demonstrated. Figure 4 shows an eye with Gelfilm in the anterior chamber, and Figures 5 and 6 are enlargements of Figure 4. Here, again, after six weeks, it is apparent that there is no inflammatory reaction. The signal lack of reaction to the Gelfilm in the eyes and the absence of any foreign body reaction make one think that the Gelfilm is dissolved by some enzy-

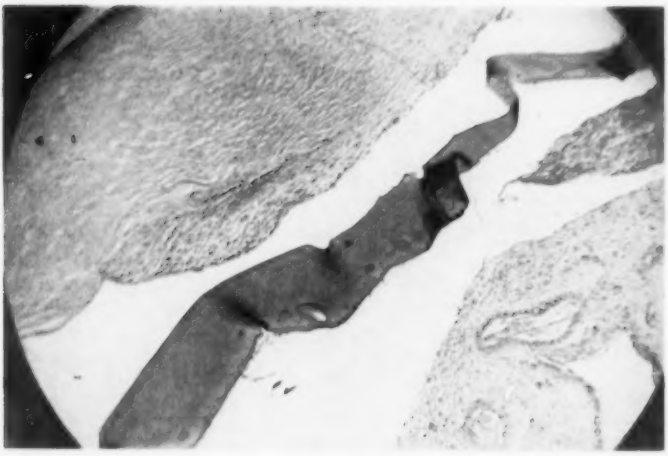


Figure 5

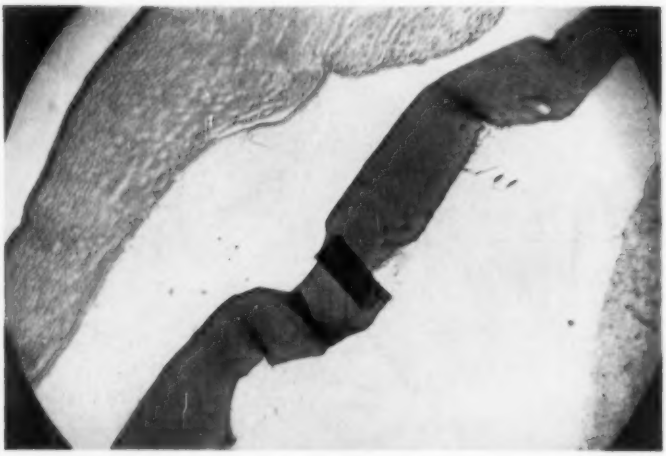


Figure 6

matic action that digests it down to component molecular elements, doing away with the mechanical reaction of an inflammatory tissue response to a foreign body.

CLINICAL APPLICATION

Encouraged by these results in rabbit eyes, in which there was no inflammatory reaction, and by the results of its use on such delicate tissues as the brain and the lung, we decided to use it in human eyes.

Our technique was as follows: The conjunctival flap was prepared as in any iris inclusion operation. An incision was made through conjunctiva 10 mm. above the limbus and through Tenon's capsule about 5 mm. above the limbus. An ab externo incision was made 2 mm. above the limbus, and the iris was withdrawn and cut across the pupillary zone. After one pillar had been allowed to retract into the anterior chamber, a piece by Gelfilm measuring 4×10 mm. was placed over the prolapsed iris pillar so as to be parallel to the limbus (Fig. 7). The Gelfilm when wet is quite pliable and falls easily into the curve of the globe. Conjunctiva and

Figure 7

Tenon's capsule were then closed with continuous 000000 chromic absorbable surgical sutures, care being taken to place the sutures close together in order to secure very tight closure of the wound. The after-care is routine for that in any ordinary iris inclusion procedure. Postoperatively, there is no undue reaction from the procedure. There is no undue inflammatory response to the Gelfilm.

The Gelfilm remains distinguishable from the time of the postoperative dressing until it is absorbed. It can be seen lying just beneath the conjunctiva. So far, we have carried out this procedure on a total of 24 patients. The first case was done 12 months ago and the most recent 2 weeks ago. In none of these cases was there any postoperative elevation in tension. In all but three the blebs which were formed were small and flat. In the three in which flat blebs did not form the filtration is excellent, as evidenced by the low tension. In the cases in which blebs formed it was noted that the Gelfilm remained in contact with the conjunctiva rather than with the iris. It is assumed that this was due to the aqueous infiltrating between Gelfilm and iris and pushing it against the conjunctiva.

In all instances the filtrating areas were much larger than normal because the length of the Gelfilm extended beyond the width of the iris wick. The Gelfilm remained visible for two to three months, as shown in Figure 8. Its disappearance is marked by absence of reaction of any kind, as shown in Figure 9.

Lately, we have also used Gelfilm in cases of detached retina. After the diathermy punctures have been made, with or without scleral or lamellar resection, and before the rectus muscle is sutured back to its original insertion, a large flat piece of Gelfilm is placed against the sclera. The muscle and conjunctiva are sewn over the underlying Gelfilm. This prevents adhesions of the conjunctiva and of the muscle to the sclera,

Figure 8

Figure 9

making secondary operations easier of performance. In the few patients in whom we have used it, we have found the Gelfilm quite fragmented and partially absorbed, with no conjunctival or muscle adhesions. This observation will be reported soon, as a separate paper. We would also suggest that Gelfilm be used in cyclodiathermy operations, in which it should be placed over the sclera after the diathermy punctures and before the conjunctiva is sewn into place. If subsequent operations should be necessary, or an enucleation indicated, as in cases of absolute glaucoma, it would be easy to dissect the conjunctiva free from the sclera.

Dr. Arnold I. Turtz performed some of the rabbit experiments; Miss Ruth Bach and Miss Sylvia Richardson prepared the eyes for microscopic examination.

This operative procedure was televised at the XVII International Congress of Ophthalmology in New York, Sept. 3, 1954.

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Characteristics of Suppression in Strabismus

ARTHUR JAMPOLSKY, M.D., San Francisco

The ability of human beings to suppress or inhibit a part of the binocular visual field in strabismus, and only that part of the visual field which is confusing to visual orientation, is a remarkably subtle property. It is a well-known fact that patients may have full binocular fusion in one position of gaze but, because of extraocular muscle noncomitancy, such as an overactive inferior oblique, may suppress a part of the binocular field in another position of gaze. The suppression is called upon only when needed. In concomitant strabismus, the region of suppression may be shown to have a border at the vertical decussation line through the macula (hemiretinal), which is its most constant, interesting, and clinically useful characteristic.

It is the purpose of this paper to emphasize the clinical advantage of simplicity in testing procedures in the determination of the characteristics of suppression in strabismic patients, to outline the quantitative and qualitative aspects of suppression by clinical and laboratory tests, and to point out the importance of the hemiretinal border (at the decussation line) in the regional suppression found in strabismus.

Hemiretinal functional differences have been mentioned on previous occasions in the literature. The extreme clinical importance of such functional differences between the nasal and the temporal part of the retina has not been fully appreciated. The recognition of such differences leads to a better understanding of the phenomena observed in examination of strabismic patients and provides a practical and useful clinical concept in treatment. The hemiretinal difference in suppression may be used advantageously in the treatment of strabismus by both the orthoptist and the surgeon as an aid in the attainment of fusion. Recognition of the usefulness of the hemiretinal border to the region of suppression in strabismus will in some cases make a difference between surgical failure and fusional cure during the immediate postoperative period.

Before the hemiretinal characteristics of suppression in strabismus are discussed, some previously known facts concerning the nature of suppression and related sensorial anomalies will be reviewed, and the factors involved in the laboratory and clinical investigation of suppression will be discussed.

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GENERAL NATURE OF SUPPRESSION

Visual suppression (inhibition, neutralization, extinction) is an active internal inhibition, and, like other sensory inhibitions, is a type of conditioned reflex.[1] Suppression is an active, acquired process of repression with a purpose, and is extremely common in binocular vision. Suppression in strabismus is a binocular act, existing only when both eyes are open and usually developed to avoid a bothersome diplopia.

CHARACTERISTICS OF SUPPRESSION IN STRABISMUS

The suppression in strabismus (*a*) is confined to a specific region or regions, (*b*) exists under conditions of binocular vision only, (*c*) may be demonstrated primarily

for similar contours, (*d*) requires a short latent period to become manifest, and (*e*) differs markedly in the developmental period before visual adulthood is reached (approximately age 6 years) and after visual adulthood. The suppression is always regional. This may be easily demonstrated by plotting the functional suppression scotoma by tangent screen methods or by demonstrating diplopia when the image in the eye with the suppression scotoma is moved to other parts of the retina by a prism placed before it. The region or area of suppression may be large or small in extent, but the suppression may not necessarily be deep. The area may be small in extent, yet the suppression may be very profound. Suppression may exist for distance fixation alone and not for near, or vice versa. Suppression is a convenient luxury that is called into use when needed.

The extent of the region of suppression may be determined conveniently by the use of a rotary Risley prism or by haploscopic targets, by techniques to be described presently.

The region of suppression exists for conditions of binocular vision only, that is, in the strabismic patient when both eyes are open with the normally fixing eye fixating an object. The region of suppression may then be plotted by binocular perimetric or tangent screen methods and is a functional scotoma found in the deviating eye under these conditions. No such scotoma is found when the deviating eye is fixating alone. In alternating strabismus the regional scotoma is found in the deviating eye only.

The regional suppression in strabismic patients may exist for similar contours only. Testing situations which alter the exact similarity of contours in each retinal image that exist under conditions of usual, everyday visual situations, may be sufficient to alter markedly the characteristics of suppression found. Quantitative, as well as qualitative, variations occur, so that suppression may also involve dissimilar contours, as well as color, light, and motion. Characteristically, however, suppression in strabismic patients exists solely for similar contours in an untrained patient.

There is a latent period associated with the phenomenon of suppression. It takes time to suppress. If an object is presented to a deviating eye so that the image falls upon a normally suppressed area, and the time of exposure is sufficiently short, the suppression may not become manifest. A brief, flashing exposure by cover test or major amblyoscope flash procedure is frequently sufficient alteration of the usual continuous bilateral ocular perception to eliminate the suppression completely. Such a brief single-flash exposure reveals interesting differences with regard to foveal phenomena in esotropic and exotropic deviations.

Diplopia may be elicited within the normally suppressed eccentric retinal area in most strabismic patients by utilizing the latent period of suppression while fixing a light source. If an opaque cover is placed before the deviating eye and removed only momentarily for a brief flash exposure of the deviating eye, diplopia sometimes may be elicited. With some acutely observing patients, extremely transient diplopia will be recognized, which quickly fades if the cover is quickly removed and not replaced. This demonstrates the presence of a latent period in the physiological process of suppression.

A similar latent period of foveal suppression may be demonstrated only in certain patients, usually exotropes. In this clinical procedure, with habitual fixation patterns in force, a brief flash exposure and prompt recocclusion of the strabismic fovea may reveal a remarkable momentary enhancement of visual acuity by the deviating fovea, as well as correct localization, while the fellow eye still maintains fixation.

Influence of Age.—The ability to establish new patterns of suppression is great diminished after the age of 6 years. This delineation is more or less arbitrary, but clinically useful. Thus, acquired diplopia in an adult patient as the result of a paretic strabismus is rarely met by the development of a region

of inhibition. The diplopia persists. The second image may be "ignored" [2] but may be consciously recognized and accurately localized if desired. This is not so in true suppression, where an actual functional scotoma may be plotted under binocular conditions.

The factor of age in suppression has other implications for the strabismic patient, for it is probable that the development of anomalous retinal correspondence is dependent upon the development of suppression. After visual adulthood has been attained, it is infrequent to note the development of new regions of suppression or the establishment of anomalous retinal correspondence. Thus, before the age of 6 years, an alternating exotrope with equal vision who is surgically converted into an esotrope may then acquire appropriate sensory changes to this new situation and ultimately become a constant monocular esotrope with amblyopia and suppression. A similar surgical overcorrection in adult life usually results in persistent diplopia.

Suppression being a perceptual pattern, the ability to acquire or change it depends upon past experience and attention. Likewise, the patient who has developed suppression early in life may find it difficult to establish new patterns later. For example, through orthoptic training in adult life, areas of suppression may be erased in the mind's eye, sometimes with disastrous visual results to the patient unless fusion is subsequently attained. In adult life suppression is a one-way street, insofar as one may erase old suppression patterns but not establish new ones.

In normal adults with full binocular fusion and normal retinal correspondence, if one eye is forcibly rotated nasally or temporally with forceps to produce a manifest strabismus, the subject becomes aware of two disturbing factors. The first is diplopia; that is, he will see the same object in two different places in space. This is because the fovea of one eye and an eccentric point in the fellow eye receive an image of the same object. Secondly, he becomes aware of another phenomenon, known as confusion. This is due to the fact that the fovea of the fixating eye and the fovea of the deviating eye each receive different images. According to the laws of visual localization, these two sharply defined, different images will be perceived as if localized in the same place in space. If it were possible, in the squinting eye, to suppress the image at the eccentric area on the retina, which is received sharply defined by the fixating fovea, the diplopia would be eliminated. Only a relatively small area in the deviating eye would have to be so blotted out or suppressed.*

If, now, one could blot out or suppress the image on the fovea of the deviating eye, the confusion would also be eliminated (Fig. 1). Indeed, just such a thing occurs in a child with strabismus. As previously discussed, an infant has a remarkable power of actively inhibiting the image received by certain areas of the retina in order to eliminate disturbing factors in his visual orientation. Such suppression may develop with great facility and be easily altered during visual infancy, after which time the visual patterns are sufficiently fixed that it is rare for new areas of suppression to develop.

CLINICAL MEASUREMENT OF SUPPRESSION IN STRABISMUS

In the past, the major amblyoscope, the Worth four-dot test, and other, more complicated clinical tests have been used to determine the presence or absence of suppression in a strabismic patient. These tests usually add little knowledge to the simple observa-

* Reference 3. In the English literature there is no appropriate term to describe the eccentric retinal area in the deviating eye upon which falls the same image as that received by a fovea of the fixing eye. This has been termed the *Deckstelle* by Linksz. It is the "retinal area" which is "covered" in the squinting eye by the image of the fixation object. Since this area is usually determined by appropriate measurements with prisms or haploscopic devices, such as the major amblyoscope, we shall use the descriptive term "zero measure point" to describe the "straight-ahead position" or the position of the eccentric point in the deviating eye which receives an image of the object fixated by the fovea of the fellow eye, with zero setting of the major amblyoscope, or with zero prisms used in the cover test procedure (Fig. 1).

tion that if an untrained strabismic patient, when observing an ordinary light under casual conditions of binocular vision, in a well-lighted room with both eyes open, without the use of any instrumentation, reports that only one light is seen, he therefore must be suppressing some retinal areas.

The determination of the exact characteristics and extent of the suppression area, however, presents a different problem, for suppression or inhibition is one of the subtlest and most alterable properties of all sensorial anomalies. In order to measure these characteristics, one must have the conditions of testing very precisely simulate that of casual, everyday seeing. This qualification is not met in many of the complex clinical and laboratory testing situations, with consequent confusion resulting.

Alterations of any of the following variables during clinical testing procedures may modify, or even completely eliminate, suppression.

(*a*) Fixation. One should have the usually fixing eye fixating during the measurement, without a conscious effort toward altering the usual fixation relationships. Altering the color of the image seen by one eye may be sufficient to establish diplopia. Any method utilizing colored filters or lights may be a sufficient change to prevent proper examination of the exact characteristics of suppression.

(*b*) Peripheral fusion. Elimination of the full expanse of peripheral fusional stimuli frequently affects the character of the axial and hemiretinal suppression. There is some evidence to show that a peripheral fusional stimulus has a differential effect upon the suppression existing in convergent as compared with divergent deviations. It should be remembered that the major amblyoscopes in common use limit the effective field to approximately 20 degrees in extent.

(*c*) Training of patient. An untrained patient gives more valuable information as to the character of suppression than one who is aware of various possibilities in the procedure, or one who has been repeatedly tested. The initial measurements made in the determination of the suppression characteristics may be the most accurate, despite the desirability of repeated tests for statistical evaluation.

If all the possible check marks for suppression are pointed out to the patient prior to testing, a very different result may be obtained as compared with the examination of a completely naïve patient. Once tested, one may no longer have the same visual conditions in the patient.

(*d*) Attention. Altering or redirecting the attention of the patient being tested may affect the determinations. Retinal rivalry and suppression are closely related to the factor of attention. Therefore, the results may be significantly altered by directing the patient's attention to some particular aspect of the testing situation. For example, strongly directed attention to a particular contour in a haploscopic target before one eye may result in a relative loss of normal retinal rivalry. This, therefore, is a type of suppression.

(*e*) Differential impressiveness. A difference in illumination, or sharpness of contour and resolution, may be sufficient to direct attention to one of the two retinal images and thereby affect suppression determinations. Any dissimilarity of contour or color may induce retinal rivalry or may enhance or eliminate existing suppression. In the examination of the exact characteristics of suppression in strabismus, one must maintain exact similarity in the object of regard and avoid procedures which may alter the similarity of the images formed in the two eyes.

It is to be emphasized, therefore, that, in order to elucidate the exact characteristics of suppression in strabismus, the conditions of testing must simulate everyday seeing patterns as closely as possible, because of the possibility that even slight alteration in any of several variables may grossly affect the results. By meticulously designed examination we may force the suppression to vanish into obscurity.

An example of this is the Worth four-dot test, which utilizes red-green goggles and colored lights, without peripheral visual stimulation, and is often done in a dark room under conditions not ordinarily existing in habitual seeing patterns. It has already been noted that simple alteration in color may completely eliminate the suppression. With the usual-size four-dot test, there is appreciable separation of the colored lights, and it is possible to miss a rather significant area of suppression. This is best exemplified by patients who have a small angle of esotropia (of about 5△), with an actual deviation, who may "fuse" all the dots correctly and be misinterpreted as being without suppression and with full binocular fusion. Many of these cases, especially those with nonaccommodative postoperative esotropia, can be demonstrated to have a manifest strabismus with anomalous retinal correspondence, with suppression of both the squinting fovea and the eccentric "zero measure point," by other tests. Yet such a patient may demonstrate no suppression with good "fusion" by the gross four-dot test.

Smaller Worth four-dot tests, with a small total subtense, are available and often lead to a different interpretation. The usual Worth four-dot test is but a gross determination of suppression and, in my opinion, has a doubtful place in the armamentarium to determine the presence or absence of suppression. It is superfluous at times to depend upon an artificial laboratory experiment which may lead to misinterpretation of the facts of suppression when common-sense deduction may be more profitable.

Historical Review.—There have been many attempts to measure the areas of suppression in strabismus, with regard to the extent and characteristics, by both laboratory and clinical procedures. A. Graefe [4] was one of the first to show that there was "regional exclusion" in the squinting eye. Travers [5] contributed a very comprehensive study of the different regions of suppression in strabismus by utilizing a laboratory setup consisting of a perimeter and colored filters before the eyes, with colored lights to differentiate the images seen by each eye. With this and similar laboratory procedures, he was able to demonstrate that under conditions of binocular vision in strabismic patients there is an area in the squinting eye which receives the image of the object fixated by the nonsquinting eye that characteristically is suppressed. Such a suppression area exists in the squinting eye only under conditions of binocular vision. If the strabismus is of an alternating type and the fixation is changed so that now the fellow eye is the deviating eye, a similar functional scotoma will be found in the now deviating eye. No such scotoma is found monocularly. Occasionally, especially in amblyopia, Travers was also able to demonstrate an area of suppression corresponding to the strabismic fovea. Travers found the foveal area of suppression more difficult to measure and demonstrate under the conditions of his experiment. These and many other experiments by Travers were fundamental landmarks in the understanding of suppression in the binocular act of strabismic patients. At that time the necessity of maintaining exact conditions of casual seeing when determining the characteristics of suppression was not fully appreciated.

Fifteen years later, in commenting upon the work of Travers, Linksz † wrote:

> We do not question the results arrived at by Travers and other workers in this field. They did find some kind of scotoma. The trouble is in the philosophy of such experiments, such atomistic experiments which forget about the total investigative situation while allegedly testing the behaviour of localized retinal elements. Squinters don't usually run around with slanting mirrors placed against one of their eyes or with red and green goggles. In case you place a small slanting mirror in front of my right eye, preventing it from fixating the target fixated by my left eye, and if you then move some object, say a pin, across the screen (a tangent screen observed only by the right eye), presenting it to my right fovea, I, too, get a functional scotoma whenever the image of your pin moves across my right fovea. The two foveas cannot ever "see" two things in exactly the same focus. One of them will always

† Linksz,[6] p. 575.

give way. For this I don't have to be an alternating squinter.

These comments emphasize the point that such highly artificial laboratory set-ups used in the measurement of suppression in binocular vision are subject to the difficulty that the exact characteristics of the suppression may be difficult to elucidate. Nevertheless, the treatise by Travers was a large step forward in our understanding of the nature of suppression.

RISLEY PRISM TEST

The qualitative and quantitative characteristics of strabismic suppression may best be measured under ordinary visual conditions by a device which does not alter any of the variables mentioned in the foregoing discussion. Although a perfect test is not realizable for clinical purposes, a hand-held Risley prism acceptably fulfills most of the requirements. This simple clinical method, with the patient unencumbered by colored glasses or filtered lights, with the usual fixation habits under room illumination, reveals some interesting facts. Under such circumstances the absence of diplopia in the presence of an unmistakable strabismus indicates the presence of suppression of the "zero measure point." In such cases it may usually be assumed that the onset of strabismus was during visual infancy, when suppression was capable of establishment. The presence of diplopia under such circumstances may indicate an inability to suppress, or a visually trained patient, or a strabismus with onset after visual adulthood. By means of a noncolored Risley prism placed before the deviating eye, one may measure the extent and depth of the region of suppression. With the patient fixing a distant light in the primary plane under the conditions described above, the amount of vertical prism before the deviating eye is gradually increased. An amount is soon reached whereupon the patient becomes aware of diplopia. Similarly, if one introduces vertical prism in an opposite direction, of an approximately equal amount, diplopia will again be observed. The depth of suppression within this region is greatest at the "zero measure point," as may be demonstrated by slightly changing the color of the image falling on "the zero measure point" by introducing a light red filter before the strabismic eye. Diplopia will usually not become evident for the "zero measure point" unless a very deep red filter is introduced to produce a greater differential in color between the two images. If the image in the deviating eye is displaced in any direction from the zero measure point by the introduction of an uncolored prism of insufficient amount to produce diplopia (within the scotoma or region of suppression), one may then elicit the presence of the second image by introducing a lightly colored filter before this eye. It was previously noted that diplopia may also be elicited by utilizing the latent period of suppression through a brief flash exposure of the deviating eye by an opaque cover, which is rapidly replaced.

The gradual increase in power of a vertically placed Risley prism in front of the deviating eye reveals that with repeated measurements the vertical extent of the area of suppression diminishes. The hemiretinal decussation borderline usually remains fixed with repeated measurements. A great many repetitions of the measurement in the vertical meridian, starting from the "zero measure point," cause a sufficient shrinkage of the border of the functional scotoma, so that eventually spontaneous fleeting diplopia may be observed without prisms. This demonstrates that each determination of the presence of suppression in any testing situation serves to make the suppression less evident and is, in effect, orthoptic training.

In a completely naive patient so tested for the first time, it will be found that the vertical extent of the region of suppression is greater if measured from within the scotoma centrifugally, as compared with a measurement from the diplopia area toward "the zero measure point." The border of the scotoma is pushed in either direction, much in the same fashion as in the tangent-screen plotting of pathologic scotomata.

The training effect of repeated measurements of suppression may be demonstrated also by the introduction of a red glass filter before the deviating eye. Sometimes a relatively few repeated introductions of the red glass before the deviating eye may temporarily eliminate suppression and establish diplopia after the red glass is removed. Indeed, an elaboration of this technique is the very method used by orthoptists to eliminate suppression in indicated cases as a part of the orthoptic training technique.

It should be emphasized that an expression of the character of retinal correspondence (normal or anomalous) is a reflection of relative localization in visual space, and should in no way be based upon the degree of suppression. There have been attempts by some authors to base the classification of anomalous correspondence upon the character and size of the suppression area at the subjective angle. This is in conflict with fundamental definitions. Every patient with constant strabismus has some suppression at "the zero measure point" if the onset of strabismus was during visual infancy and he was capable of establishing suppression. The size of the suppression area varies considerably with different patients, and is found to be very small in some cases of long-standing strabismus in so-called harmonious anomalous retinal correspondence.

Examination of the horizontal extent of the regional suppression in strabismus reveals the most interesting of its characteristics and the most clinically useful. Gradually increasing the Risley prism power in the horizontal meridian before the deviating eye will delineate an egg-shaped area of suppression bounded by a vertical line at the nasal-temporal decussation which includes the macular area on one side, and by a variable area around "the zero measure point" on the other side (Fig. 1). In equal-visioned strabismic eyes diplopia is elicited as soon as the macular vertical meridian (the hemiretinal boundary) is passed. The suppression area extends slightly further in amblyopic eyes.

It appears, therefore, that functionally there is an imaginary vertical line (decussation line) almost through the macula of the deviating eye, separating the eye into the nasal and temporal retinal areas with respect to the border of suppression, in either esotropia or exotropia.‡

It is not at all necessary to make all the measurements described above for proper clinical evaluation of the strabismic patient. However, awareness of the characteristics of the region of suppression is extremely valuable. For example, in orthoptic training to eliminate suppression, utilization of more

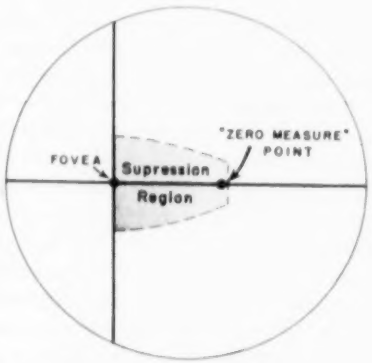

Fig. 1.—Diagrammatic representation of region of suppression on the retina of a strabismic patient.

than one of the variables, such as latent period, alteration in color, or similarity of contour, fixation, and attention, will prove more beneficial than if a single technique is used. Similarly, knowledge of the regional and hemiretinal nature of the border of suppression may be utilized in the postoperative patient with surgically undercorrected strabismus by prescribing prisms of such a strength as "optically to complete" the surgical procedure by displacing the image

‡ Linksz[3] (pp. 349 and 351) states: "It is inconceivable that such a thing as a sharp dividing vertical line should exist in the macula or the retina. . . . There can be no functional fission through the fovea just because there is a fissure between the two halves of the brain. . . . Our statistical hypothesis bids then for lack of perfect splitting of the macula and for its bilateral representation."

from within the region of suppression to the opposite hemiretina, where diplopia will be elicited. This procedure, as a temporary postoperative orthoptic measure, is of especial value in undercorrected intermittent exotropia. The important clinical utilization of the knowledge of the regional hemiretinal nature of suppression in the management of strabismus (by establishing diplopia) immediately after operation through surgical overcorrection is not always fully appreciated. Other factors, however, may sometimes contraindicate surgical overcorrection.

Clinical observations of these characteristics of suppression in strabismus have been emphasized by Posner and Schlossman.[6] They observed that a surgical overcorrection of a strabismus produces spontaneous diplopia postoperatively in most patients. Indeed, the amount of overcorrection need be only 2 or 3 △ to produce diplopia. One frequently observes patients with postoperative overcorrection of the strabismus who volunteer the fact that they are experiencing diplopia. In such a patient, if horizontal prisms, of such an amount as effectively to reproduce optically even a slight undercorrection of the strabismus, are now placed before the eyes, the diplopia disappears. The image now falls on the usually suppressed hemiretinal area.

Exceptions to the phenomenon of decussation line border of the regional suppression are cases of long-standing strabismus in adults, in whom even a small change in the angle of strabismus produced surgically may result in diplopia, regardless of over- or undercorrection. Deep amblyopia in one eye may also obscure these findings.

Further characteristics of the region of suppression and its relationship to other sensory phenomena in strabismus, such as anomalous retinal correspondence, may be elucidated by using haploscopic picture targets with multiple contours utilizing the full peripheral fusional areas.

HAPLOSCOPIC TESTS

The hemiretinal regional character of suppression in strabismus may be demonstrated conveniently with the commercially available major amblyoscopes or with the twin Polaroid projection apparatus. These methods adhere more closely to the general concept of exact similarity of targets, i. e., multiple contours in pictures rather than a light source, and thus, by more closely simulating habitual seeing experiences, reveal other subtle characteristics *within* the region of suppression. The most important condition that must be met in such tests is that similar targets be used. Orthoptists have long been taught to avoid the use of similar targets in the measurement of anomalous correspondence and other sensory anomalies on the major amblyoscope because of the possibility that anomalous peripheral fusion may take place or sudden changes in the angle of deviation may occur. Especially in the realm of orthoptic treatment, these possibilities are very real indeed, and it is wise for the most part to heed these time-worn warnings, unless close check is maintained upon the relative position of the patient's visual axes. Most of these complications may be avoided by the use of dissimilar targets. However, in investigating the true character of suppression in strabismus, many interesting things may be learned by use of the major amblyoscope or the projection apparatus utilizing similar targets if one maintains control of the fixating eye and maintains careful check at all times for shifts in fixation or in the angle of deviation.

Phenomena Observed with Dissimilar Haploscopic Targets.—It has been known for some time that, although some strabismic patients may not obtain so-called first-degree fusion on the major amblyoscope (simultaneous perception of dissimilar targets), they may obtain second- or even third-degree fusion with similar targets. This is true even when careful check is made by the examiner to avoid changes in the angle of deviation, and when the full extent of the visual field of the major amblyoscope is used. In the light of the previous discussion, this really should not be surprising, since first-degree fusion, as usually measured on the major amblyoscope with dissimilar tar-

gets presented to the two eyes, is an entirely artificial circumstance. Thus, one must expect occasional bizarre findings and be cautious about their interpretation when the conditions of casual seeing have been disturbed. Dissimilar targets may cause attention to be directed more strongly toward one of the pair of haploscopically presented targets, thereby altering physiologic retinal rivalry sufficiently to simulate suppression of one target. However, the use of dissimilar targets on the major amblyoscope for the determination of the character of retinal correspondence has been advocated for good reason. Their use offers less stimulus to fusional movements, so that the angle of deviation remains relatively constant and a more accurate determination of relative visual localization may be made. In the customary manner of determining the character of anomalous retinal correspondence on the major amblyoscope with the use of dissimilar targets, one usually finds an area of suppression at the subjective angle.

Investigators have long been puzzled by the observation that the subjective angle is frequently found to be between "the zero measure position" and the objective angle rather than at "the zero measure position," as it "should" be, i.e., harmonious anomalous correspondence. Since simultaneous perception of dissimilar images is an extremely artificial circumstance, it should also not be surprising that relative visual localization becomes confused under these conditions. When the area of suppression around the subjective angle so determined is of such a depth or extent that it confuses the determination, one may use alternative methods to define it more accurately. Major amblyoscope targets are limited in extent to approximately 20 degrees, which is sufficient for the determination of the subjective angle in most patients. The peripheral expanse of the field with the use of Polaroid projection apparatus is practically unlimited. In our experience, the dissimilar targets (Fig. 3) have been found to be most useful in the determination of the subjective angle because of the absence of overlapping check marks, while including

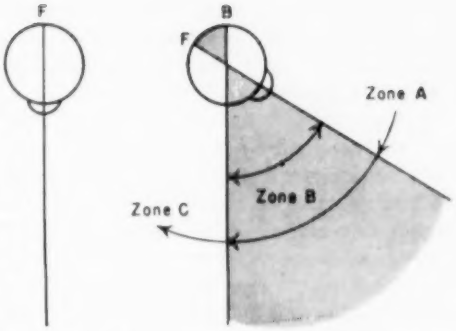

Fig. 2.—Diagrammatic representation of region of suppression (Zone B) bordered by fovea (*F*) and point *B*.

as large a peripheral area as the amblyoscope will allow. The habitually fixing eye continually fixates the small dot while the broken vertical line or circle is moved before the deviating eye for subjective alignment.

One may be aided further in the determination of the subjective angle by utilizing the latent period of suppression discussed previously, with either similar or dissimilar targets in the major amblyoscope. Fixation is maintained with the habitually fixing eye, and a larger target is presented to the deviating eye for only a brief moment by flashing exposure on the amblyoscope or projection apparatus. By this method, one remains within the latent period of suppression so that the patient sees the target briefly flashed without stimulus to fusion or chance to alter his deviation. Under these conditions relative localization is easier for the patient and suppression is seldom a problem. Circumventing the obstacle of suppression in this fashion apparently does not alter the relative locali-

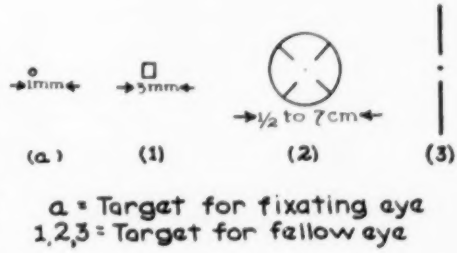

Fig. 3.—Dissimilar haploscopic targets.

zation. It is a simple matter for the orthoptist to expose the target to the squinting eye for a brief flash to various retinal areas while eliciting responses from the patient as to which side of the fixating dot it appears. By this method one may determine retinal correspondence more easily in difficult cases, and in all cases of strabismus one finds a higher percentage of harmonious anomalous correspondence and normal retinal correspondence, with a corresponding decrease in the number of unharmonious correspondence cases determined. Although this method, too, is a highly artificial circumstance, it, nevertheless, is less so than the simultaneous perception of dissimilar targets. Moreover, since the monocular flash technique, utilizing the latent period of suppression, produces more expected results insofar as they concern the type of retinal correspondence which "should" be found, it may be the preferable method.§

It is probable that the character of retinal correspondence found in strabismus is but one of the characteristics of suppression, and that an anomaly of relative visual localization may follow in the wake of suppression. The regional suppression described above is almost always found in concomitant strabismus with onset during visual infancy. Anomalous retinal correspondence may or may not develop as a part of the suppression phenomena.

§ Unharmonious anomalous retinal correspondence is an exceedingly rare finding in exotropia, and an infrequent finding in esotropia, with these techniques. Unharmonious anomalous retinal correspondence, never adequately explained on a physiologic or an autistic basis, may therefore be an artifact of our methods of measurement. If more refined methods are used and are still more closely adapted to the conditions of casual seeing, one may predict that the subjective angle would have but two reference points, namely, that of the objective angle, in which case there would be normal retinal correspondence, and "the zero measure point," in which case there would be harmonious anomalous retinal correspondence. Unharmonious anomalous correspondence may be expected to fade away some day, unexplained because it will become unnecessary to explain it.

Phenomena Observed with Similar Haploscopic Targets.—If one uses large similar targets on the major amblyoscope or Polaroid projection apparatus, one observes some most interesting phenomena with respect to (1) suppression, (2) relative localization, (3) recognition of contour, and (4) the hemiretinal nature of these in both normal and anomalous retinal correspondence (Fig. 2). With similar targets in the major amblyoscope, with maintenance of fixation by the habitually fixating eye (right eye, Fig. 2), and with the arms of the major amblyoscope set at an angle greater than the angle of deviation (Zone A), the targets will be seen *simultaneously* and each *described* and *localized* accurately. There is good *recognition* of both targets in Zone A even if the image falls a considerable distance from the fovea of the deviating eye. If, while maintaining fixation with the right eye, the target before the deviated eye is moved a given increment over the retina, the patient will be able to tell that it has been moved a certain proportional amount within Zone A. The extent of motion is perceived accurately. The relative localization in this zone is definite and exact. If one moves the fixated target before the right eye a given increment, the patient will again describe a proportional movement correctly.

With the habitually fixating right eye always fixating, if the target before the deviated eye is now moved toward the macula into Zone B, marked confusion is experienced by the patient. This is especially true in exotropia, where the eyes may proceed to alternate fixation rapidly and it will become difficult for the patient to maintain constant fixation with the usually fixating eye. On the other hand, the target of the deviating eye may be completely suppressed as soon as it is moved into the other hemiretinal area by crossing the decussation line at the macula. If the targets are both perceived, they are usually not seen truly simultaneously with Zone B. Although the patient may have difficulty in verbalizing the nature of what he is seeing and how it differs from true simul-

taneous perception, such as occurs within Zone A, it is evident that they are not the same. This is particularly true in exotropia and occurs to a less extent in esotropia.

Within Zone B the similar target presented to the deviating eye may be completely suppressed. If both targets are perceived "at the same time," the target before the deviated eye may not be *recognized* accurately and the details and contours of this target are not easily *described*, even though it is fairly close to the fovea. The patient may state that he knows there is a target present, but he cannot tell exactly what it is. Now, if the target before the deviating eye is moved a certain increment within Zone B, the patient cannot accurately describe the proportional movement which occurred, but is vaguely aware that it has been moved. If the target before the fixating eye is moved a certain increment, the patient will accurately and satisfactorily describe the movement.

The character of relative localization of the targets in Zone B is often most confusing, and, again, is most marked in exotropia. Patients frequently cannot describe the relative localization of two targets perceived in space, even though definitely aware of two separated targets. There is a part, if not all, of Zone B in which there is confused localization, or in fact lost localization. This must be differentiated from anomalous localization, in which the patient describes well the relative positions of two targets perceived in space, albeit localized anomalously. With confused or lost relative localization, two separated targets are perceived in space with an inability to describe which one is situated to the right and which one to the left, a seemingly incongruous situation.‖

The marked changes in the subjective sensorial phenomena described ¶ upon crossing the hemiretinal decussation line through the macula are so striking that they can afford an accurate means of clinically measuring the actual relative position of the foveas, or, in other words, the objective angle. When similar targets are used at greater than the objective angle and slowly moved toward the objective angle while the patient is maintaining fixation with the habitually fixating eye, he will become confused when the imaginary decussation line is crossed. In exotropia there may be rapid alternate fixation, as well as suppression; but in esotropia, usually only relative suppression. When passing over the imaginary vertical raphe (or decussation line) in this manner, the patient may be able to describe a change from uncrossed to crossed diplopia (or vice versa), even though there is relative suppression, in which case there is normal retinal correspondence. The relative suppression, confusion in localization and in recognition which takes place at the decussation line, occurs regardless of the presence of normal or anomalous retinal correspondence.

The hemiretinal character of the relative suppression does not extend over the entire half-retina, and its extent may be demonstrated by the following: The separation of the amblyoscope arms is now further decreased to approach "the zero measure point," into Zone C (Fig. 2), where diplopia is again established. The similar target before the deviated eye emerges from its relative or complete suppression, and in Zone C the two targets are now perceived again truly simultaneously. The confusion Zone B therefore extends from the objective angle (macula) to the zero angle (zero measure point) under conditions of binocular vision which as closely as possible approximate everyday visual situations.

The peculiar sensorial phenomena taking place within this zone may not be recognized at all if these conditions are upset, as by the use of dissimilar targets. With the use of dissimilar targets, only the most profound changes which occur in Zone B, such as around the zero measure point, or subjective angle, will be observed, and the borders and other confusion phenomena become ill

‖ Cf. Reference 7. Ronne has termed this "projectional agnosia."

¶ The terms extinction, obscuration, mislocalization, and displacement have been used by neurologists to describe similar phenomena in neurology. (Bender.[9] Reider.[10] Furmanski.[11])

defined. There is considerable variation in the character of Zone B in different patients with strabismus. Not all reveal the "type reaction" described, there being degrees of relative suppression.

One may delineate the borders of Zone B more precisely if, rather than moving from Zone A to Zone B, as described (Fig. 2), one begins from somewhere within Zone B where the suppression is the greatest. Progressing from within Zone B toward Zone C or Zone A, that is, toward the zero measure point or toward the macula of the deviating eye, one progresses from the relatively suppressed toward the nonsuppressed area. The complete or relative suppression will terminate more precisely at the border of Zone A and Zone C if done in this fashion. Going from Zone C or Zone A toward Zone B "pushes in" the borders of the area of suppression and makes them less clearly defined. It will be noted, therefore, that this suppression area will behave much in the same fashion as in the plotting of any pathologic scotoma in ordinary clinical perimetry or tangent field studies of nonstrabismic patients. This same phenomenon was obtained in measurements with the Risley prism. It is well recognized that one may "push" the border in the direction of measurement and that, for ill-defined scotomata in the visual field, working from within the "blind" area toward the "seeing" area produces more accurate and consistent determination of the border of the scotoma. A similar situation exists for the determination of the boundaries of the regional suppression (Zone B) in strabismus.

The latent period of suppression may be utilized to clarify the relative localization of similar targets within Zone B. If the similar target before the deviating eye within Zone B is presented for only a brief flash exposure, suppression is entirely eliminated and relative localization becomes more accurate. With steady, simultaneous, continuous exposure of the similar targets, it again fades into relative or complete suppression. A brief flash exposure eliminates suppression of either similar or dissimilar targets without apparently altering the relative localization.

COMPARISON OF SIMILAR AND DISSIMILAR HAPLOSCOPIC TARGETS

The differences in the character of the various zones when similar and dissimilar targets are used has been pointed out. A further examination of these differences within the suppression Zone B is of interest. With similar targets an area of maximum confusion within Zone B is selected and the amblyoscope or projection apparatus is locked in this position. In cases with marked suppression only the target before the fixating eye will be clearly described by the patient. If the suppressed similar target before the deviating eye within Zone B is now replaced with a target dissimilar to that seen with the fixating eye, but of the same size, the two may now be seen without suppression or alternation of fixation, described clearly, as well as localized accurately. Replacing the similar target in the same position before the deviating eye results in its being completely suppressed. If it is now replaced with a dissimilar target, but of even smaller size, the suppression is again eliminated and both targets will be perceived. With the similar target replaced, it is again suppressed, even if the illumination is increased considerably. This is a very frequently demonstrable phenomenon, although not invariable. Its occurrence merely confirms the fact that suppression in the binocular visual act is related to form and contour and may be unrelated to size, color, illumination, and other components of vision. Hamburger # reported similar findings in his examination of strabismic patients with anomalous retinal correspondence. He observed that with the use of targets having both similar, fusionable contours and dissimilar contours, patients with anomalous correspondence suppressed the similar parts of the target at the objective angle while

Reference 8; cited by Burian, H.: Strabismus: Annual Reviews, A. M. A. Arch. Ophth. **46**:81 (July) 1951.

describing the presence of the dissimilar parts of the target. They did this even though the dissimilar part was not joined to the main part of the figure, although it was localized at some distance from it in a rather indefinite way, according to whether unharmonious or harmonious anomalous correspondence existed.

Variants. — The above description, of course, is of a general pattern and serves only to emphasize general principles. There are many exceptions to and variations of the typical reactions, and clear-cut unchangeable delineations may not be made. For purposes of clinical usefulness it may be an advantage to be somewhat dogmatic in description, so long as one realizes the exceptions and general character of the processes involved. It is of importance to point out the rather marked and consistent differences in delineation of the various zones described in cases of esotropia when compared with cases of exotropia.

The following is but one example of a variant reaction pattern with respect to the various zones described. In some patients with exotropia, with similar targets in the major amblyoscope or projection apparatus, passing from Zone A to Zone B (Fig. 2) may not produce the change in relative localization such as would be expected in normal retinal correspondence. The target before the deviated eye is always localized ipsilaterally. As the zero measure point is approached, one would expect a change in relative localization along the way at "some" position at or between the zero measure point and the fovea. There "should be" some position of a subjective angle in order to determine either normal or anomalous correspondence. However, some exotropic patients continue to localize the target before the deviating eye ipsilaterally even within Zone C, and, in fact, in any position on the retina. With repeated testing, but without coaching, some of these patients with confused localization suddenly seemingly become aware of unknown cues, and alter their reports of relative localization to describe either normal or harmonious anomalous correspondence.

Variation from the "type reaction" may also occur in patients with an amblyopic strabismic eye. The hemiretinal border may be quite ill-defined because of the scotoma demonstrable in the macular area of most amblyopic patients.

Regardless of whether the retinal correspondence is found to be normal or anomalous, the hemiretinal border of the region of suppression remains fixed. In exceptional cases, with adult strabismus of very long duration, the region of suppression may be confined to a small area around the zero measure point and the fovea. The change in relative localization, however, may occur either at the fovea (normal retinal correspondence) or at the "zero measure point" (harmonious anomalous retinal correspondence), but the suppression and confusion are always bounded on one side by the foveal line, and, less consistently, on the other side by "the zero measure point." There are noticeable quantitative and qualitative differences between esotropia and exotropia relative to the confusion Zone B. The curious observations with regard to relative localization found in exotropia when compared with esotropia serve to emphasize the important differences in the sensorial changes found in these two very different types of strabismus. General discussions of strabismus (especially statistical) should clearly differentiate between the sensorial anomalies found in esotropia and in exotropia.

SUMMARY

Visual suppression, under binocular conditions of strabismus, may be demonstrated for similar contours, but not necessarily for other components of vision.

There is a latent period of suppression in strabismus which may be used to advantage in the examination and determination of relative localization with either similar or dissimilar amblyoscope targets.

The results of the usual clinical tests to determine the presence or absence of suppression in strabismus are often confusing and superfluous.

Suppression in strabismus exists only under the precise conditions of usual, everyday visual situations. One may demonstrate a region of suppression confined to the nasal retina in esotropia, and to the temporal retina in exotropia, bounded by a vertical line through and including the macula, on one side, and the "zero measure point" (*Deckstelle*), on the other side. Within this region there may be relative or complete suppression, obscuration, confused or lost relative localization, mislocalization, or displacement.

Qualitative differences exist between esotropia and exotropia with regard to the regional sensorial anomalies described, but are independent of the presence or absence of anomalous retinal correspondence.

Anomalous retinal correspondence is probably one of the characteristics of the suppression phenomenon. When suppression is established early in the strabismic patient, anomalous retinal correspondence may or may not follow in its wake.

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Digital Pressure, an Important Safeguard in Cataract Surgery

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It is the prime purpose of this communication to emphasize, on the basis of clinical experience, the very great importance of the use of digital pressure as a safeguard against vitreous loss in cataract surgery. Secondly, preliminary evidence is presented as to the mechanism of action of digital pressure in the production of this clinically observed increased safety.

The first reference to the use of digital pressure following retrobulbar injection in intraocular surgery was by Atkinson [1] in 1934, who stated:

> For a few moments slight pressure is exerted on the globe with a little rotary motion, so that the procaine solution is more thoroughly diffused within the muscular cone.

Our interest in this problem began when one of us (R. E. K.) visited in Boston and observed the routine use by Chandler of five minutes of pressure following the retrobulbar injection. Chandler * wrote: "I hit upon the idea of pressure over the eye and lids some years ago and have used it ever since." There have been a number of references to the use of massage and/or pressure following retrobulbar injection, but these have all been made in passing, as it were, in papers concerned with more general subjects. Atkinson † mentions briefly the use of gentle massage in each of his papers on ocular anesthesia, as do Guyton [5] and Jensen,[6] in writing about complications of cataract surgery, and deRoetth and Carrol,[7] in their study of the effect of retrobulbar procaine injection on aqueous humor dynamics. It was not surprising to learn, therefore, after a canvass of many of our colleagues, that the use of digital pressure is not widespread. Vail,‡ Wendell Hughes,§ and Adler and Scheie ‖ state that they do not use digital pressure in their cataract surgery, the last indicating that "we do use hyaluronidase along with a local anesthetic, and feel that we get a satisfactory anesthesia as a result of this." Furthermore, digital pressure was not employed by Snydacker, Deutsch, and Bayard [8] in their study devoted to anesthetic agents in retrobulbar injections. Indeed, it is of interest to note that Gifford,[9] in a study relating chiefly to the lowering of ocular tension and vitreous pressure, makes no mention of the use of digital pressure. For these reasons, it seems important to contribute a paper primarily concerned with the documentation of the facts learned by a clinical and experimental study of the effects of digital pressure following the retrobulbar injection in cataract surgery.

PLAN OF STUDY

Early in our clinical experience with the use of digital pressure in cataract surgery it became apparent that factors were operating to reduce greatly the intravitreal pressure; this was evidenced chiefly by the observation that, as the lens was tumbled, the anterior vitreous face could consistently be seen as a markedly concave surface, the iris plane was

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* Chandler, P. H.: Personal communication to the authors.

† References 2 to 4.

‡ Vail, Derrick: Personal communication to the authors.

§ Hughes, Wendell: Personal communication to the authors.

‖ Adler, F. H., and Scheie, H.: Personal communication to the authors.

positioned more posteriorly than usual, and the cornea was usually collapsed. It became necessary, therefore, to attempt to determine, first, whether these factors really constituted a safeguard against vitreous loss and, if so, to investigate whether they were related to decreased intraocular pressure, decreased intraorbital pressure, decreased retrobulbar volume, or a combination of these circumstances.

MATERIALS AND METHODS

I. *Clinical Study.*—The incidence of vitreous loss in 100 consecutive cases of cataract surgery performed by us after we began the routine use of five minutes of digital pressure following the retrobulbar injection is recorded. This is compared with the incidence of vitreous loss in three 100-case series of cataract extractions performed by us after the introduction of the use of hyaluronidase in the retrobulbar injection but before our employment of digital pressure.

II. *Experimental Study.*—The effects of five minutes of digital pressure (applied to the eyeball after the retrobulbar injection) upon the intraocular pressure, the intraorbital pressure, and the exophthalmic state of the eye were studied. These studies were performed both in the office prior to cataract surgery and in the operating room during the course of the actual cataract operation. The intraocular pressure was recorded with the Schiøtz tonometer; the intraorbital pressure studies were performed with the Copper orbitonometer, and the degree of exophthalmos was measured with the Hertel exophthalmometer. In the operating room during the course of cataract operations, the tonometer, the orbitonometer, and the exophthalmometer were sterilized for repeated use during the course of the surgery. These studies were performed upon 8 eyes in the office and upon 14 eyes in the operating room during cataract surgery. When it became apparent from these 22 cases that the only significant changes were in the intraocular pressure, the orbitonometry and exophthalmometry were abandoned. Further intraocular pressure studies were then performed on an additional 7 eyes (representing a total of 15 eyes) in the office prior to cataract surgery and upon an additional 36 eyes in the operating room, thus affording data on 50 eyes studied during the actual surgical procedure. Various control studies are included, namely, studies upon the fellow (intact) eye during the course of cataract extraction in its mate (from which evidence was also adduced as to the duration of the hypotonic effects under actual operating conditions), the effect of retrobulbar injection without digital pressure, and, finally, the differences in effect upon the same eye with the patient fully awake preoperatively in the office as compared with the patient under heavy sedation during the actual cataract surgery.

The orbital tension measurements were made according to the method of Copper [10] except that the elastic headband of the Copper orbitonometer could not be sterilized for use in the operating room, so that it was removed from the instrument. The orbitonometer was then held in place against the bridge of the nose and the external canthal angles by an assistant. E_0 (zero indentation), E_1 (intermediate indentation), and E_2 (maximum indentation) readings were taken after application of the contact shell to the globe and the total displacement (T. D.) calculated.

Bilateral Schiøtz tonometry, orbital tonometry, and exophthalmometry were performed together at the start of the procedure, immediately after the retrobulbar injection, and immediately after the application of five minutes of digital pressure. In 15 operating room cases measurement of the ocular tension was further continued in the intact eye by an assistant at regular intervals while the surgeon proceeded with the cataract extraction in the fellow eye.

The technique of application of the digital pressure was as follows: In the operating room the corneoscleral sutures were preplaced, and the retrobulbar injection was performed after the insertion of these sutures. Immediately upon withdrawal of the retrobulbar needle the lids were closed and two fluffed 4×4 gauze bandages were placed over the closed lids. The flat surfaces of the tips of three fingers of the left hand were placed over the gauze; the similar fingers of the right hand were placed atop the left fingers, and quite firm, steady digital pressure was thus applied for five minutes by the clock, the pressure being released for two seconds every one-half minute to insure against occlusion of the retinal vessel. Immediately thereafter, the tonometric and exophthalmometric readings were repeated, and the operation was continued.

The anesthetic agent used chiefly was 2% lidocaine (Xylocaine) with epinephrine and hyaluronidase, although comparative studies were performed in several cases, using 2% or 4% procaine with epinephrine and hyaluronidase.

RESULTS

I. Clinical Study

In 100 consecutive cases of cataract surgery performed by us after we began the routine use of five minutes of digital pressure following the retrobulbar injection, operative loss of vitreous did not occur in a single instance. The incidence of vitreous loss in

TABLE 1.—*Non-Operating-Room Measurements of Intraocular Pressure (in Millimeters Schiøtz) Following Retrobulbar Injection and Digital Pressure*

Case	Initial	Post-retrobulbar	Post-digital	Minutes Remaining Under 10 Mm. Schiøtz
1	20.1	20.1*	0	14
2	16.0	17.0*	0	12
3	20.1	23.4*	4	7
4	21.8	20.1	4	8
5	23.4	20.1	11	0
6	20.1	20.1	8	2
7	16.9	16.9	8	2
8	16.9	16.9	5	8
9	16.9	11.9	0	7
10	18.5	13.2	9	3
11	18.5	20.1	0	10
12	21.0	21.0	9	1
13	21.0	21.0	8	1
14	18.5	18.5	8	10
15	18.5	18.5	0	20
Average	19.2	18.6	4.9	7

* 2% procaine (with epinephrine and hyaluronidase) used.

three 100-case series of cataract extractions performed by us prior to our employment of digital pressure, but after beginning our use of hyaluronidase in the retrobulbar injection, varied from 3 to 4 cases of vitreous loss per 100-case series.

II. EXPERIMENTAL STUDY

(*a*) *Non-Operating-Room Experiments.*—1. Effect on Intraocular Pressure: Table 1 summarizes the data. In 15 cases the average initial tension (in millimeters, Schiøtz) was 19.2, the average tension immediately after the retrobulbar injection was 18.6, and the average tension immediately after five minutes of digital pressure was 4.9. In 5 of the 15 cases the ocular tension fell, after digital pressure, to 0 mm. Schiøtz (tonometer scale readings of 14 or more), while the highest tension recorded in this series was 11 mm. In the average case the tension remained under 10 mm. Schiøtz for 7.0 minutes.

2. Effect on Orbital Tension: From the data recorded in Table 2 it is seen that the orbitonometer readings and the total displacement produced in each instance were approximately the same (except in Case 5) for

TABLE 2.—*Non-Operating-Room Measurement of Orbital Tension*

Case	Degree of Change	Initial		Postretrobulbar		Postdigital	
		Exptl. Eye	Control Eye	Exptl. Eye	Control Eye	Exptl. Eye	Control Eye
1*	E_0	15.5	16.0	15.5	15.0	16.0	14.5
	E_2	12.0	12.0	11.0	12.0	12.0	12.0
	E_4	10.5	10.5	10.0	10.0	10.5	9.0
	T. D.	5.0	5.5	5.5	5.0	5.5	5.5
2*	E_0	11.0	13.0	11.0	12.0	11.0	12.0
	E_2	6.0	9.5	7.0	8.0	7.0	8.0
	E_4	5.0	8.0	5.5	7.0	6.0	7.0
	T. D.	6.0	5.0	5.5	5.0	5.0	5.0
3	E_0	14.2	12.7	14.0	14.0	14.0	14.1
	E_2	12.0	10.0	11.0	11.5	11.0	11.5
	E_4	9.8	7.0	8.0	8.7	8.0	9.0
	T. D.	4.4	5.7	6.0	5.3	6.0	5.1
4	E_0	11.2	10.5	9.2	10.0	9.1	10.8
	E_2	9.0	8.0	6.0	8.0	7.0	8.0
	E_4	7.0	6.0	4.9	6.0	5.0	5.2
	T. D.	4.5	4.2	4.3	4.0	4.1	5.6
5	E_0	12.5	12.1	9.0	8.6	8.4	9.0
	E_2	10.1	9.2	7.2	6.3	7.5	7.5
	E_4	8.5	6.1	5.2	4.4	6.1	4.9
	T. D.	4.0	6.0	4.8	4.2	2.3	4.1
6	E_0	15.0	15.5	15.0	15.0	14.5	16.0
	E_2	10.8	10.0	10.0	10.0	11.0	11.0
	E_4	8.0	9.0	7.5	8.0	9.0	9.0
	T. D.	7.0	6.5	7.5	7.0	5.5	7.0
7	E_0	10.2	10.2	11.0	10.0	9.9	11.0
	E_2	8.3	8.0	8.4	8.4	7.3	7.0
	E_4	5.2	6.0	6.0	5.4	5.1	6.4
	T. D.	5.0	4.2	5.0	4.6	4.8	4.6
8	E_0	12.8	12.5	12.6	10.5	12.0	11.8
	E_2	10.3	10.4	11.2	9.1	9.7	9.0
	E_4	8.1	8.2	8.3	5.5	7.5	6.4
	T. D.	4.7	4.3	5.3	5.0	4.5	5.4

* 2% procaine (with epinephrine and hyaluronidase) used.

both the experimental eye and the control eye (the latter having had neither retrobulbar injection nor application of digital pressure). From these data it may be concluded that there is no significant change produced in the orbital tension under these conditions.

TABLE 3.—*Operating-Room Measurements of Intraocular Pressure (in Millimeters Schiøtz) Following Retrobulbar Injection and Digital Pressure*

Case	Initial	Post-retrobulbar	Post-digital	Minutes Remaining Under 10 Mm. Schiøtz
1	17.0	14.0	0	20
2	14.2	14.2	0	..
3	15.6	15.6	2	..
4	11.0	11.0	0	..
5	17.2	10.0	0	..
6	23.5	23.5	0	18
7	18.0	7.0	0	..
8	15.6	8.0	2	..
9	18.5	4.0*	0	..
10	17.0	20.0	4	14
11	14.2	8.0	0	..
12	17.0	8.0*	0	..
13	13.2	8.0*	0	..
14	20.0	20.0	9	12
15	11.0	18.5	8	3
16	11.0	4.0	0	..
17	20.1	11.0	1	..
18	20.1	21.8	10	0
19	14.2	14.2*	8	..
20	20.0	10.0	6	..
21	20.0	15.6	6	17
22	17.0	21.8*	6	8
23	20.0	6.2*	0	..
24	17.0	9.0†	0	..
25	17.0	23.4†	3	17
26	10.0	4.0	4	..
27	10.0	17.0	4	11
28	14.2	6.2	0	..
29	14.2	5.0	0	..
30	20.1	17.0	4	15
31	17.0	9.0	6	..
32	15.6	15.6	4	..
33	14.2	14.2	9	4
34	17.0	11.9	0	30
35	17.0	14.2	0	..
36	15.6	4.0	2	..
37	15.6	11.0	3	22
38	17.0	13.2	6	..
39	10.0	7.0	0	..
40	15.6	11.5	0	..
41	18.5	17.0	4	..
42	17.0	10.0	4	..
43	15.6	4.6	0	..
44	14.2	14.2	3	11
45	14.2	8.0	7	..
46	18.5	10.0	0	..
47	17.0	11.5	0	..
48	18.5	13.2	0	..
49	18.5	8.0	0	..
50	17.0	14.2	0	..
Average	16.2	11.9	2.3	14.3

* 4% procaine (with epinephrine and hyaluronidase) used.
† 2% procaine (with epinephrine and hyaluronidase) used.

3. Effect on Exophthalmometry: In eight cases, the average initial Hertel reading was 17.5 mm., the average reading immediately after the retrobulbar injection was 18 mm. and the average reading following five minutes of digital pressure was 17.5 mm. Six of the eight cases followed this average change very closely, while two of the cases presented a decrease of 1.5 mm. in the readings taken after application of digital pressure as compared with those taken after the retrobulbar injection.

(b) Experiments in Operating Room.—1. Effect on Intraocular Pressure: Table 3 summarizes the data obtained on the 50 eyes investigated during actual cataract surgery. The important facts are that, while the initial and postretrobulbar tensions are moderately lower than those in the nonoperating room group (Table 1), the intraocular pressure in the average case in the operating room decreased to 2.3 mm. Schiøtz. Moreover, in 27 of the 50 cases the ocular tension was zero, and this represented in many cases tonometer scale readings of 16-20 (in other words, 0—). Finally, the tension remained under 10 mm. Schiøtz in the operating room for an average of 14.3 minutes in the 15 cases investigated for duration of the effect, while in the 15 cases investigated outside the operating room the average duration under a tension of 10 mm. Schiøtz was only 7 minutes.

Table 5 summarizes the data of a control experiment in the operating room wherein the effect of omission of digital pressure in one eye was studied. Three cases in which cataract extraction was to be performed upon the right eye were selected, and the right eye was subjected to the usual lid akinesia, retrobulbar injection, and five minutes of digital pressure. The left eye was simultaneously subjected to lid akinesia and retrobulbar injection, but no digital pressure was applied. Table 5 indicates clearly that, although there is a small decrease in ocular tension with the retrobulbar injection (as is well known and as particularly studied by Gifford,[9] Snydacker

TABLE 4.—*Summary of Operating-Room Measurement of Orbital Tension (Fourteen Cases)*

Case	Degree of Change	Initial		Postretrobulbar		Postdigital	
		Exptl. Eye	Control Eye	Exptl. Eye	Control Eye	Exptl. Eye	Control Eye
Case with greatest change	E_0	13.0	12.0	13.2	15.0	12.0	11.0
	E_2	10.0	9.5	10.0	11.0	9.5	8.5
	E_4	8.5	8.5	8.5	9.5	8.3	7.5
	T. D.	4.5	3.5	4.7	5.5	3.7	3.5
Case with least change	E_0	12.0	12.0	12.1	12.0	10.2	12.2
	E_2	9.2	9.6	10.0	10.5	7.2	10.0
	E_4	8.5	8.8	8.6	8.6	6.5	8.5
	T. D.	3.5	3.2	3.5	3.4	3.7	3.7
Average case	E_0	14.7	15.0	14.9	15.5	13.2	13.8
	E_2	12.3	12.5	12.0	12.2	11.5	11.0
	E_4	9.4	10.0	9.9	10.3	8.1	8.4
	T. D.	5.3	5.0	5.0	5.2	5.1	5.4

and associates [6] and deRoetth and Carrol [7]), there is produced in the fellow eye a much more profound hypotony with the application of digital pressure.

2. Effect on Orbital Tension: In the 14 eyes investigated during cataract surgery the orbitonometry results followed closely the results obtained in the office experiments. Because of this it is not deemed worth while to tabulate all of the data; we wish simply to summarize the data (Table 4) by recording the findings in the case with the greatest changes in orbital tension and total displacement, in the case with the least changes, and, finally, in the mathematically average case. It is seen here, as in the non-operating-room cases, that no significant change in orbital tension is evoked under the circumstances of this investigation.

TABLE 5.—*Effect on Intraocular Pressure (in Millimeters Schiøtz) of Lid Akinesia and Retrobulbar Injection Without Digital Pressure (in Operating Room)*

Case		Retrobulbar Injection and Digital Pressure (Right Eye)	Retrobulbar Injection Without Digital Pressure (Left Eye)
1	Initial	18.5	16.9
	Postretrobulbar	13.2	14.6
	Postdigital Right eye only	0.0	11.0 *
2	Initial	15.6	14.2
	Postretrobulbar	9.0	17.0
	Postdigital Right eye only	0.0	14.2 *
3	Initial	13.0	13.6
	Postretrobulbar	11.9	12.0
	Postdigital Right eye only	0.0	9.0 *

* Five minutes after retrobulbar injection.

3. Effect on Exophthalmometry: In the 14 eyes studied in the operating room the results of exophthalmometry were similar to those obtained from the 8 eyes investigated in the office experiments. No variation of more than 1.5 mm. Hertel was observed, and it is concluded that no significant change in the exophthalmic state of the eye occurs under these circumstances.

(*c*) *Comparison of Effects on Same Eye Preoperatively and During Operation.*—Table 6 summarizes the data in four cases. It will be noted that, although in one case the postdigital-pressure tonometric reading was the same both in the office and during surgery, in general there was a relative hypotony in the operating room. Our local anesthesia routine consists of moderate barbiturate sedation and intravenous meperidine (Demerol) injection to the point of moderate narcosis, and this may be a factor contributing to the hypotony. Moreover, there is some evidence in the present study to indicate that, apart from the akinesia, the surgical manipulations incident to dissecting the conjunctiva and the limbal grooves and incident to placing

TABLE 6.—*Comparison of Effect on Intraocular Pressure (in Millimeters Schiøtz) Preoperatively with Effect on Same Eye at Time of Cataract Surgery*

Case	Preoperative			Operating Room		
	Initial	Postretrobulbar	Postdigital	Initial	Postretrobulbar	Postdigital
1	21.0	21.0	8.0	16.9	19.0	3.6
2	16.9	16.9	8.0	14.2	14.2	8.0
3	23.4	21.8	11.0	16.9	16.9	6.6
4	20.1	20.1	4.6	11.9	11.9	0.6

the corneoscleral sutures are in themselves creative of more hypotony. Such evidence was a consistent small lowering of tension when measured before and after these surgical manipulations.

That the systemically administered barbiturates and meperidine may have a profound effect on ocular hypotony is indicated by one case wherein the patient was overnarcotized and became apneic. Following resuscitation the anesthetist gave assurance that the operation could continue, and it is worthy of note that the ocular tension remained under 5 mm. Schiøtz for more than 35 minutes after the application of digital pressure.

COMMENT

As stated initially, it is the chief purpose of this study to emphasize, on the basis of clinical experience, the great value of the use of digital pressure as a safeguard against vitreous loss in cataract surgery. We are aware that the presentation of 100 consecutive cases of cataract operation without vitreous loss since our inception of the application of digital pressure, even when compared with the incidence of vitreous loss in our previous three 100-case series, does not constitute scientifically unimpeachable proof of the value of digital pressure. However, when the evidence is considered in the light of the other data obtained in this study, it is felt very strongly that digital pressure does constitute an important safeguard in cataract surgery.

In almost every case there was convincing evidence that the intravitreal pressure was markedly reduced. As the lens was tumbled, the anterior vitreous face was consistently seen as a markedly concave surface, with spontaneous aspiration of an air bubble into the anterior chamber. Moreover, the plane of the iris was positioned more posteriorly, and the cornea was usually collapsed. Although these findings were sometimes in evidence prior to our use of digital pressure, the consistency of this observation with the use of digital pressure was remarkable. There were approximately 5 cases in the 100-case series in which the anterior vitreous face and iris diaphragm were not far posterior but came forward against the cornea after delivery of the lens. The vitreous pressure even in these cases must have been lowered adequately, for there was neither rupture of the anterior vitreous face nor operative vitreous loss.

The simultaneous investigation of ocular tension, orbital tension and exophthalmometry have indicated that the safety-producing site of action of digital pressure lies not in the orbit but within the globe itself. As to the mechanism of its action, the only objective evidence adduced thus far is that there is a great decrease in intraocular pressure and a decrease in intravitreal pressure. How these are brought about remains to be elucidated. Moreover, whether the reduction in intraocular pressure always parallels, and can be used as a criterion of, reduction in vitreous pressure is also not yet known. For the present, it can be stated that the marked ocular hypotony is at least associated with increased protection against operative vitreous loss.

In this regard, it is important to observe that, in the operating room, the intraocular pressure remained under 10 mm. Schiøtz for an average of 14.3 minutes. Since the time elapsed from completion of the application of digital pressure to completion of the lens extraction averaged about nine minutes, the presence of continuing hypotony at the critical moment of tumbling of the lens is appreciated.

One case deserves description as emphasizing further the increased safety that is associated with the use of digital pressure. During a lens extraction the patient coughed and raised his head just as the lens was being tumbled, and there was an instantaneous expulsion of the lens. Despite this, the anterior vitreous face was immediately seen to be concave and in its far-posterior position.

It is noteworthy that no complication resulted from the additional manipulations necessitated by the investigation in the operating room. Moreover, no complication was

encountered from the use of digital pressure, such as subluxation of the lens. The prevention of retrobulbar hemorrhage by the application of digital pressure immediately after the retrobulbar injection needs only be mentioned, and the gradual production of hypotony by digital pressure appears in theory to be a safeguard against expulsive choroidal hemorrhage, which might otherwise be favored by the sudden hypotony produced in opening a firmer eye. It was our observation that early in our surgery on such soft eyes more lens capsules than usual were being ruptured but, as Atkinson ¶ writes, with increasing experience this is overcome, probably by confidence that one may use more hook pressure with equanimity.

Finally, it is hoped that sufficient evidence has been presented to encourage the universal use of digital pressure as a safeguard against vitreous loss, the most dangerous of avoidable complications in cataract surgery.

SUMMARY

Clinical and experimental evidence is adduced to emphasize the great importance of the use of digital pressure as a safeguard against vitreous loss in cataract surgery.

The site of the safeguarding action of digital pressure is localized, and preliminary evidence is presented as to the mechanism of action.

The application of digital pressure to the eyeball after retrobulbar injection is followed by a profound ocular hypotony and lowering of intravitreal pressure. In the operating room during cataract surgery the intraocular pressure decreased, in the average case, to 2.3 mm. Schiøtz; in over half the cases the tension was 0 mm. Schiøtz, and the average duration of intraocular pressure below 10 mm. Schiøtz was 14.3 minutes. Control experiments indicate that this degree and duration of hypotony are lacking in eyes not subjected to application of digital pressure.

On the basis of the evidence at hand, it is strongly recommended that the application of five minutes of digital pressure to the eyeball following retrobulbar injection be adopted as a routine and vital safeguard in cataract surgery.

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¶ Personal communication to the authors.

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Magnification

Practical applications of the Principles of Magnification to the Problems of Subnormal Vision

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Many patients with subnormal vision who have been relegated to a nonvisual life can be rehabilitated with proper magnifying devices. While most of these devices are applicable to near-vision problems only, some are useful for distance functions. There is nothing new or mysterious about the principles and application of magnification in the problem of low vision. Nevertheless, this has been one of the most neglected fields in ophthalmology. The ophthalmological literature of the past years is comparatively devoid of articles relating to the application of magnifiers in the field of visual rehabilitation.

MAGNIFICATION

Anyone who does not have sufficient vision to perform efficiently his daily home or work tasks with ordinary spectacle-glass correction may be considered a candidate for low-vision aids.

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New York Hospital-Cornell Medical Center (Dr. Gordon), American Foundation for the Blind (Mr. Ritter).

This work is being continued at the New York Hospital under a grant from the National Council to Combat Blindness, in cooperation with the Low Vision Project of the American Foundation for the Blind.

It is not within the province of this paper to discuss the pathology responsible for low vision.

While we are accustomed to thinking of legal blindness in terms of Snellen vision or perimetric studies, these means alone do not suffice to give a true picture of the patient's visual potentiality. The visual potentiality is based, for the most part, upon the amount of retina destroyed. Hence, it might be said to be a combination of central and peripheral vision plus the size and number of scotomata present.

One obtains his visual impression of an object as a result of its image as formed on the retina. The closer the object is held to the eye, the larger is the image seen and the greater the amount of detail noted. Obviously, there is a distinct limit within which one cannot bring an object. However, if one now interposes the proper plus (convex) lens between the eye and the object, one is able to see it clearly at a closer range.

There is a difference between the function of the lens which is employed for the purpose of magnification and one which serves as a reading addition. Pascal, in a personal communication, has stated that the function of the reading addition is to make up for the loss of accommodative powers and to enable the patient to see again at the normal reading distance.

Any magnification produced by this reading "add" is purely incidental. On the other hand, the sole purpose of a magnifying glass is to produce magnification, that is, to increase the apparent dimensions of the objects viewed.

Any lens (or combinations of lenses) which, when used to view an object, creates the illusion of an increased dimension is a magnifier. Magnification is a function of plus lenses.

The number of magnifying devices is legion. Each has a different purpose and is efficient in direct proportion to its proper utilization. There is no such thing as the "best" magnifying glass. The choice of a device is entirely dependent upon the specific purpose for which it is required. Important considerations in guiding selection[1] are power, or magnification; working distance; field of view, and depth of field. Each of these factors varies with the others, and each tends to modify the others.

A simple formula for determining the power of a magnifying device is found by dividing the factor 10 by the focal length of the lens.

$$\frac{10}{F} = \text{power, or magnification}$$

In dealing with magnifiers, one considers the focal length of the lens and the working distance for which it is used as essentially synonymous. The focal length is actually the distance between the lens and the object when the image is sharply defined. A lens with a focal length of 2 in. is a 5 × or 5-power lens. The 10 in the formula represents 10 in., which is the average minimum distance for the normal unaided eye. This is an accepted standard. Four diopters is equivalent to 1 unit of magnification.

In selecting a magnifier, it is important to consider the working distance for which it is needed. When that is known, as can be seen from the formula above, the rest of the determination is almost automatic. It makes for greater efficiency if one can employ a magnifying glass which is of less power than that demanded by the working distance. In other words, if the working distance calls for a 3-power lens and if one could use a 2.5-power lens, one will be able to work with it more efficiently. The reasons for this will become obvious as we progress.

The field of view afforded is also a major consideration. The diameter of the field of view of any specific magnifying device is less than its focal length. It has been shown that as the strength or power of a magnifying device increases, its focal length or working distance decreases. Similarly, as the magnification increases and the lens diameter decreases, an automatic decrease in the field of view results. The question frequently arises as to why a large-diameter lens with a very high power cannot be made. It is because the sharpness of curvature of the lens surface determines the power.

Every lens is a segment or section of a sphere (Fig. 1). The curvature of the spherical surface is dependent upon the radius of that sphere. The larger the radius of curvature, the larger the sphere and the less sharp the surface curvature. On the other hand, the smaller the sphere, the smaller the radius of curvature and the sharper the surface curvature, and hence the greater the magnification afforded by a lens sectioned off that sphere. As one attempts to increase the magnification, one must use lenses cut from progressively smaller spheres, resulting in progressively smaller magnifying glasses. This statement does not apply to aspheric lenses, which can be molded from plastic. However, this process still requires considerable development. If one sphere has a radius of curvature 10 times as great as a

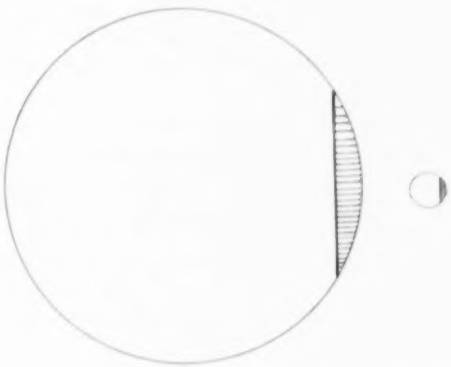

Fig. 1.—The smaller the radius of curvature of a lens, the sharper the curvature and the greater the magnifying power of the section cut off from it.

second sphere, according to the laws of optics the second sphere has a magnification power roughly 10 times that of the first.

Photographers are very aware of the importance of depth of field. They know that the closer the camera is held to the object, the smaller is the depth of field and the more precise the focus needed in order to take a sharp picture. The same statement applies to lenses. The stronger the magnifying glass, the more essential it is to hold it at a rigidly fixed distance because of the lack of depth of field. The depth of field of a magnifier may be defined as being equivalent to the distance between which one can move the magnifier to and away from the object viewed and still maintain the object in reasonably clear focus. The depth of field varies with the power of the lens. The lower the power, the greater the depth of field, and vice versa.

A lens magnifies speed in exactly the same manner as it magnifies the apparent size of the object viewed. Therefore, if one is watching moving objects with a magnifying glass of considerable high power, it is conceivable that the magnification of the speed of motion would be such as to cause the object to come in and out of the field of view too rapidly to be seen.

In dealing with magnification, one must bear in mind not only the power of magnification but the amount of separation of the letters, words, or objects viewed. Thus, in reading, if the separation of the individual letters is not sufficiently great to render each distinct, one would not be able to read.

The light and light source are of utmost importance in the use of magnification. If one reads normally, the ordinary light source coming in over the shoulder usually suffices. However, as has been pointed out above, it is necessary to stay within the focal length or working distance of the magnifying device. This means that one is usually reading at a distance of only a few inches or less, where it becomes increasingly difficult to get the light in with sufficient intensity to be helpful. This difficulty can be obviated either by having the light come in directly from the side or by having it built into the magnifier itself. It is important, in fitting a patient with any magnifying device, to be certain that he will use at least as much light when he employs the lens outside the office as when he was fitted with it.

The importance of adequate light source is illustrated by a patient with diabetic retinitis proliferans. With a +27.00 lens she was able to read Jaeger 5 in the clinic, where a frosted "bull's-eye" bulb provided the light source. When an ordinary 60-watt bulb was used in a lamp with a polished white-coated reflecting surface, she read the same size type with a +14.00 lens.

Insuring the proper light source can be very troublesome. It is common knowledge that an increase in the light makes for a decrease in the strength of the lens necessary and for a consequent increase in the field of view.

CLINICAL APPLICATION

The normal eye cannot possibly picture the needs of the abnormal one or evaluate any lens or magnifying device in the light of what it will do for a specific low-vision case.

The paramount rule in the handling of the low-vision patient is that one must not write that patient off as hopeless without a good attempt at fitting him with some reading or distance device.

Available Devices

The following low-vision aids are presently available:

1. Spectacles with high reading additions of as much as 10-12 D. or more (as bifocals, reading glasses, or the Policoff type lens)*
2. Magnifying glasses with or without supporting devices, and with or without built-in illumination (Fig. 2)
3. Projection instruments which give magnifications of as much as 25 × (Fig. 3)
4. Contact glasses, with and without the use of other vision aids
5. Telescopic lenses (distant and near vision); monocular only for near vision
6. Microscopic lenses (near vision only), monocular only

* American Optical Company has just introduced a similar type low-vision lens set.

Fig. 2.—Some ordinary hand magnifiers. These are usually 1½ to 2 powers in strength.

High Plus Additions.—As a rule, the maximum addition which is prescribed in routine refractive practice is a +2.50 or +3.00 lens. Many patients who cannot read otherwise will be benefited by reading additions of as much as +20.00 or more. Usually it will not be necessary to go above +10.00 or +12.00. Where the visual acuity is subnormal, but well above 20/200, as, say, 20/50, an intermediate addition on the order of +5.00 may be satisfactory. While this is something that "everyone knows," it is surprising how many patients in this category come into subnormal-vision clinics without ever having had a trial with this amount of addition.

It is important to caution these patients that they must hold the reading material quite close to their eyes in order to see, i. e., within the focal length of the lens. Here, again, the stronger the addition, the closer it must be held and the smaller the field. It is advisable to determine the patient's exact reading needs, and then fit him with the weakest lens that will be satisfactory. A good light source coming in from the side is a "must" when he employs these lenses.

When high plus lenses or magnifiers are employed at very short working distances, the ordinary light sources will often not suffice. The light must come in from the side in these cases. Each 4 D. of plus lens is equivalent to 1 power of magnification.

When high plus lenses are employed at very short working distances, binocularity is impossible. This is rarely a problem, as many of these patients have but one "good" eye. Adds of +6.00 or more tend to render binocular use impossible because of the short reading distance.

Fig. 3.—The Megascope of the American Foundation for the Blind. This can magnify 12 or 25 times. The reading material lies on top of the instrument on a plastic plate and is moved back and forth by use of the metal bar. The print is projected onto the glass screen. The book on top and that at the side are the same, with the print magnified 25 times on the screen.

The Policoff † lens is often valuable where a high plus add is needed. It is light in weight and excellent optically. It consists of a small, highly corrected segment, up to 14 × (56 D.) in strength, cut into an ordinary glass or plastic lens.

Hand Magnifying Lenses.—Hand magnifying glasses come in a variety of forms, some of which will be described briefly.

Large-diameter, low-power reading lenses of the Sherlock Holmes type rarely give much benefit to patients with correctable sight of less than 20/200. About 5-power (+20.00 lens) is usually the minimum strength which is useful. A British lens,‡ mounted on a plastic stand, which maintains a fixed normal working distance, has been found useful in this strength. The plastic lens, which is aspherically formed, permits the eye to be held at considerable distance from the lens with little distortion.

A nominally 5-power doublet lens system,§ with a flashlight or an electric light introduced into the side of the barrel on which the lenses are mounted, to maintain the proper working distance, has also been found popular. In both these devices, the lens measures about 1⅞ in. in diameter, providing a greater field than is ordinarily available in this strength. The illuminated magnifier actually gives a magnification of about 8 powers. (More can be had if the eye is moved away from the glass, a procedure which causes great peripheral distortion but which is, nevertheless, beneficial to many users.)

It should be noted again that the normal eye is not able to predict the value of any lens or lens combination for the abnormal eye. It is common experience to present the patient with two different devices of the same strength and have him select the optically inferior one. A combination of lenses which satisfies the low-vision patient may reveal only a meaningless blur to the normal eye.

A weaker system which has proved useful to many with 15/200 to 20/200 visual acuity is a pair of 2½-power (10.00 D.) lenses ground on prisms to simplify convergence.‖ They are mounted in headbands. The same lens mounts, fitted with 5 or 7 D. systems, may have some applications. The latter is available with an additional monocular 10 D. add, which swings into place when required. They can also be used occasionally in combination with desk magnifiers, such as the 2-power Burton Fluorescent Magnifier or Dazor system.

Inexpensive magnifiers, mounted on tripods, with the lens housing threaded to permit focusing, are available in strengths of from 7 to 10 ×. A number of legally blind persons have removed these from the tripod and mounted them in a pair of inexpensive frames (sunglasses with one of the dark-glass pieces broken out). This arrangement has been found as satisfactory to some patients as the much more expensive telescopic spectacles with reading caps, or microscopic lenses.

A 10-power system with the lens housing threaded to move in and out of a barrel has a penlight built into one side to give illumination and serve as a handle.¶ This has proved to be one of the most popular magnifying devices now in use, some patients gaining facility enough to read entire textbooks.

The cheap folding magnifiers, originally put out by Bausch & Lomb and widely imitated, have had considerable acceptance. The model most commonly used is a dual 3- and 3.5-power lens, combinable to give a total strength of 6 powers. It has good field and helps many borderline cases. Two-ply systems, giving combined strengths of 8 and 10 powers, respectively, are available in smaller lenses. A three-ply device, giving a maximum of 20 powers, has many devotees. Occasionally a patient reports inserting the 8-power version behind his regular glasses.

Magnification alone does not appear to be an adequate explanation for the value

† Policoff, W.: Personal communication to the authors.

‡ The Plasta Cataract Reader.

§ The Adisco Illuminated Magnifier.

‖ No. 10 Magni-Focuser.

¶ Flawfinder (E. W. Pyke & Co.)

of a lens to a given patient. For example, a two-power planoconvex glass of French # origin, has been the device of choice for some persons with as little as 5/200 vision. Such persons usually depend upon their peripheral vision. For most patients with macular lesions the value of good field and good contrast seems especially important. This planoconvex lens rests directly on the page and concentrates an unusually high amount of ambient light upon the text. Where it alone is inadequate, it may be used under the Burton Fluorescent Magnifier or coupled with any other hand magnifier of a strength up to 5 powers, although 3-3½ powers seems to give the best results in most cases. The version which has proved most useful is about 2 in. in diameter. A larger version is almost universally rejected, either because of light loss which is noticeable even to the normal eye or because of greater surface reflection. This lens has proved a favorite with a number of our retinitis pigmentosa patients.

Patients with macular disease or with retinitis pigmentosa dislike glare. They will shy away from illuminated magnifiers which have white or silvered side-walls in their housings. On the contrary, those with optic atrophy want considerable light concentration and may prefer these.

Jeweler's loupes worn like a monocle, clipped onto glasses, or clamped to the earpieces (Behr loupe) have their advocates. They are both inexpensive and readily available. Linen testers in 7- or 10-power strength are also readily available at low cost. At least two other 4 × * monocular loupes can be worn over spectacles.

It should be noted that stands to maintain focus, as well as to provide illumination, are included in the design of many of the aforementioned devices and may account, in part, for the preference many patients exhibit for these as against very high plus spectacles.

The supports, too, often present a method of adding a guide line, such as a thread on the 5-power plastic lens or a black line drawn with a china-marking pencil across the bottom of the planoconvex lens. Such lines are valuable in preventing the patient from losing "his place."

Adjustable masks which blot out all but the line being read are valuable for people who have very limited fields, and who would otherwise be constantly losing their "place."

The ophthalmologist traditionally has been biased in favor of something which can be worn on the face as against something which is hand-held. There are many reasons why a hand magnifier may prove more satisfactory to a patient than heavy spectacles.

1. The hand magnifiers may cost substantially less. The economic factor must be considered.
2. The distance at which a text is held from the eye may be normal, whereas strong spectacles involve bringing the page closer.
3. For a given strength, they may lend themselves to binocular reading.
4. Magnifiers with stands release the patient from the necessity of focusing. Where tremor is present, this may be a deciding factor.
5. The hand magnifiers may strike the patient as being less conspicuous. Persons without visual anomalies often use such devices. They were not designed to overcome visual impairments originally.
6. They may provide other properties which render them superior to anything so far available in spectacle form, for a specific purpose.

For these reasons, one should not be surprised if a patient, after the best that can be done with existing procedures, still prefers a simple hand magnifier. Rather, the practitioner will do well to have on hand an assortment for the patient to try. This can be done before and again after refraction, especially if much cylinder correction is indicated.

With the newly blinded, particularly, the role of hand magnifiers is important. A patient who is completely unprepared to accept his visual limitations will often learn to employ a strong lens of this sort as an interim measure. It may keep him at work. Later, the practice he has derived makes him a far easier case to fit with spectacles.

Plano-Convex Lens (St. Gaobain).

* A. S. Aloe Co. and National Optical Co. loupes.

Again, those who have been blind for a long time may be willing to use a device of this sort, so that they can develop their visual functions to the point where the minimal magnification can be prescribed.

It is well known that patients' vision behaves in an unpredictable manner. One will find many patients who are seeing things that, by all the rules in the book, they should not be able to see. It behooves us to devote more thought to the fundamental nature of low vision.

These people learn to rely upon visual cues. When the optical apparatus has very poor resolution, one learns to omit details and draw conclusions accordingly.

The newly impaired patient is unlikely to be happy with anything without an explanation. It should be pointed out that the healthy eye does not inspect. Few of us, unless we are printers, are even aware of the existence of digraphs.† For the visually impaired, digraphs present a new problem. But since the mind tends to synthesize, it is not a problem for very long.

It is also reassuring to point out that if the patient sees anything—even occasional letters—it is worth his "playing along" for a week or so. Many who see nothing at first later learn to read quite well.

It is regrettable that we are unable to predict unerringly which hand magnifier will best suit each patient. Until good clinical controls can be set up, such information will not be available. At this stage all that can be said is that each device has its own properties and field of use.

Projection Devices.—The restriction of field at higher magnifications, as well as the problems of illumination introduced, can be partly overcome by opaque projection devices. Those used for lecture purposes are not convenient because the reader, in approaching close to the screen (as he must with low vision) blocks the light. It is desirable, therefore, to bend the rays with mirrors so that the image may be projected from behind the screen.

† A digraph is a union of two characters representing a single sound, as oa in boat.

The Franklin Institute has designed such an instrument, which is being put into production under subsidies by the American Optical Company. This gives 3 to 5 powers of magnification and has its main value for those with visual acuities above 15/200.

The American Foundation for the Blind's Megascope, giving either 12 or 25 diameters of magnification, is of use to those with greater visual losses. Some with vision of approximately 2/200 have occasionally been able to read for limited periods with the 25-power version. The poorest results occur in very advanced cases of retinitis pigmentosa or high myopia. Contrary to expectations, some with as much as 20/200 vision have been willing to put up with the inconvenience of manipulating the Megascope. Perhaps this is because, once the operation has become a habit, they are able to read in a relaxed manner at a good distance from the screen.

This expensive device is not well known, as yet. It is not conveniently portable. At least three of our patients with advanced optic atrophy and vision of approximately 2/200 to 3/200 find it very convenient. Two of these are college students, who were required to hire readers prior to their introduction to the Megascope.

Contact Lenses.—Contact glasses have their chief value in correcting cases with high degrees of astigmatism (keratoconus, etc.), corneal scarring, or high myopia. It may be necessary to employ in addition one of the other aids for near vision.

Telescopic Lenses.—Telescopic lenses are employed primarily for distant vision. When reading caps are applied, they can be used for near vision. They can be utilized binocularly for distance and monocularly for near. The newer telescopic lenses are more presentable cosmetically than the older forms; the use of plastics has lightened their weight. Good telescopic and microscopic lenses are expensive. The Kollmorgen[2] telescopic lenses come in 1.7 and 2.2 powers of magnification. Obviously, the 1.7 power lens has the larger field. As with all telescopic

spectacles, the patient's refractive correction is incorporated in the proximal portion of the lens, and the reading cap, when needed, is added in front. Most patients for whom this system is prescribed will be satisfied with the +8.00 reading cap. The Univis telescopic lens is smaller than the others, resembling a small telescope cut into the center of a lens; and hence the telescope can be "looked around." The field is small. It comes in 1.5 and 2 powers. The plastic Feinbloom telescopic lens, which is lighter in weight than the Kollmorgen lens, comes in 2.2 powers only. The telescopic spectacle with the weaker reading addition is often recommended for those requiring an increased reading or working distance. This is especially true when the device is needed for such tasks as drawing, sewing, and machine work. Before a definite prescription is given, a high plus lens may be tried in comparison, since this may meet the specific requirements of a given job—architectural drawing, for example. Many patients with visual acuity somewhat better than 20/200 find the wider-angle, lower-powered, 1.7 × telescopic lens efficient for their needs. Few patients can walk about with telescopic spectacles because of the restricted field and the apparent displacement of the image, as a result of the telescopic parrallax. These lenses may be invaluable in the theater or for television, where the patient himself is not in motion.

The percentage of legally blind persons who have accepted telescopic spectacles for distance use is still low. The loss in field may not seem to be worth the slight enhancement of cues resulting from strengths of less than 3 powers.

There are on the market inexpensive, light-weight sport glasses which are essentially 2.5 to 3.5-power opera glasses with earpieces. Reading caps can be fitted to these and are useful to persons with little sight. A 6-power telescope, resembling in size and appearance a pocket flashlight, enables many to identify buses, and to read street signs or house numbers.

Higher powers, in monocular form, have been found very helpful by many who are not aided by telescopic spectacles. A 10-power prism monocular can be used by some who are not aided by the telescope. It fits comfortably in the pocket. While locating an object and holding the glass steady takes practice, this lens has become part of the standard equipment of very many "blind" people.

Larger, inexpensive monoculars of 8×30, or even 10×50, design are often used for watching television, theater performances, or ball games. Their major drawback is that they cannot be focused at close range. Weak plus additions supplied as caps might be used to overcome this. In a few cases, such devices have been mounted on laboratory stands with +1.00 to +10.00 D. caps to permit inspection of work at high magnifications. In one instance it was reported that this arrangement enabled a man to do delicate soldering operations, working under the glass.

Microscopic Lenses.—Microscopic lenses (Feinbloom and Bechtold)‡ involve the use of two or more plastic lenses plus air spaces and are for near vision only. They are employed in front of one eye only. Incidentally, this feature of microscopic lenses, (or telescopic lenses for near vision) is usually no problem, since a high percentage of patients with subnormal vision have but one useful eye. Because of the extreme degrees of magnification provided here, the reading material must be held very close to the lens; hence sufficient convergence for binocularity is impossible.

The Feinbloom lens comes in strengths up to 20 ×; the Bechtold, to 14 ×. When one multiplies these figures by 4, one obtains the equivalent dioptric designation for a convex lens. High convex lenses create too much aberration, as compared with the corrected and comparatively aberration-free micro-

‡ Feinbloom, W.: Personal communication to the authors. Bechtold, E.: Personal communication to the authors. Freeman,[3] Hellinger, G.: Personal communication to the authors.

scopic lenses. The Policoff and new American Optical Company's lenses are an exception to this rule and are cheaper.

Comparatively few patients require microscopic lenses unless very high plus is indicated. Bechtold has projected a telemicroscopic lens which combines the best features of the telescopic and microscopic lenses, permitting reading at more normal distances.

History

Much has yet to be done in developing a good routine for the handling of the low-vision patient. Actually, the term "routine" is a misnomer, since one cannot routinize this type of examination, but must tailor it to the needs and specifications of the patient. However, an attempt will be made to lay down a working plan for the ophthalmologist to employ in handling low-vision patients.

A good history will often aid in determining whether the patient can be helped and in indicating in what direction the examination should be slanted.

The points to be stressed are the following:

1. Diagnosis.
2. Duration of the disease.
3. Educational background.
4. Whether the patient can read now or could read once.
5. Occupation before and after visual loss.
6. Visual need. For what purpose does the patient want his glasses? (This is most important.)
7. Which is the better eye?
8. Is the patient now using any special devices, or has he ever been examined for any such? (It is obvious that one can waste a great deal of time in examining a patient for a magnifying device only to find that the patient either has that device or had one and did not like it, etc.)
9. How much can the patient see now; i. e., can he see headlines, large newspaper type, small newspaper type, etc.?
10. Can the patient walk about alone: (*a*) indoors or (*b*) outdoors?
11. Does he see better in bright daylight or in twilight?
12. Does the patient really want to read, or is he being forced into this by his family?

The answers to all of the above questions will give the examiner a fairly good picture of the patient's physical and psychological set-up. The patient whose visual loss is of recent date will object to the employment of abnormal reading positions. He wants to see as comfortably as before and will not go to any great trouble to learn new reading positions. As a matter of fact, most of the patients in this category still want a cure, and not a glass.

If the patient has had his defective vision for a great many years, he may already have fallen into a blind pattern. He may be well adapted to the use of Braille. He probably has been babied by his family. The main point here is that he may have very little incentive to go to the trouble of learning to read again. He may require the aid of a social service worker to redevelop such an incentive.

By this time he has probably become a visual illiterate. He can spell the words, but when he sees with some magnifying device, he does not recognize them. This patient must be retaught to read. If the physician does not realize this, he is apt to fit the patient with too strong a lens. The patient may read only Jaeger 7 when first fitted. As he learns to read again, he may rapidly come to a point where he can read fairly small type with the same, or even a weaker, lens.

The patient's ability to walk about alone is a clue to his visual field. The patient with poor central vision and absolutely no peripheral field is difficult to handle because much of the magnification depends on the ability to utilize the perimacular retina. But if none is present, then a good part of the battle has been lost in advance. This ability to walk about is also a clue to whether he has night blindness or not.

Patients who have difficulty in bright light usually have either a central scotoma or some opacity in the media, such as a cataract. The reverse, dim vision in twilight or poor light, tends to implicate the peripheral retina. If the patient can read headlines or better, he obviously is a good candidate for a low-vision aid. If he can read headlines but cannot read any print smaller than that, he may be benefited by a 2.2 × telescopic spec-

tacle. If he can see subheadlines, then he may be able to get by with 1.7 × telescopic spectacle. If he cannot read headlines, then he is going to need something in the way of an extremely high plus or microscopic lens, or a combination of a high plus lens and a magnifying device. All this information gives a working clue.

Examination

The examination, as has been said, should be slanted in the direction of the patient's needs. The patient may want his device only for use on one phase of his work. If that is the case, it is important to know just what that is so that the device can be tailored to his need, employing the principles of magnification outlined above. If the patient wants something for use in the distance and wants to walk around while wearing it, his problem at the present moment is almost insoluble if he cannot be fitted with a spectacle lens. Few patients can walk around while wearing telescopic lenses. This must be explained to him very fully. Patients resent paying for devices which they cannot employ in a practical fashion.

If one is able to provide the patient with loaners or devices on a "money-back" basis, the problem will often be simplified. Many a device which seems perfectly satisfactory in the office proves to be equally unsatisfactory when subjected to use. For the same reason, one should hesitate to give any complex prescription on the first visit. The examinations require great patience as the patients fumble in their attempts to see.

The patient should be brought back at least once or twice before the final prescription is given. Frequently the second or third visit will indicate a need for much less magnification than was apparent at the time of the first examination.

The first step is a precise objective refraction. After that the examination is aimed in the direction of the patient's need, i. e., whether distant or near function is required.

The ordinary Snellen charts do not lend themselves well to the examination of patients who have vision of less than 20/200 or even 20/100. The disparity in size between 20/200 and 20/100 is much too great for most of them. Attempts to use this type of chart at 20 ft. (6 meters) do not make for an accurate refraction. The physician should employ a chart containing letters of as high as 20/800 § (Fig. 4) or more. This examination is best done with the chart illuminated and held either by an assistant or suspended from a gooseneck lamp at a distance of 8 to 10 ft. (2.4 to 3 meters) from the patient.

When the patient is given refraction at this working distance, one can often obtain more precise information, especially as to the amount and direction of the cylinder. If one can possibly do the refraction combined with the employment of telescopic lenses, altering the cylinder, its axis, and the sphere in the trial frame behind the telescopic lens at a distance of 8 or 10 ft., a much more precise refraction can be gained. At the same time, the patient receives a great psychological impetus by observing a marked increase in his distance vision. This is true whether or not he will ultimately employ telescopic lenses. Information concerning the cylinder is of great importance if one will ultimately employ a high plus lens. If one does prescribe a telescopic lens, then the information data concerning both the sphere and the cylinder are equally important. If a microscopic lens is to be employed, then this information is of no value.

Fig. 4.—Special chart for refraction of low-vision cases. The chart is in loose-leaf form with symbols decreasing downward from 20/800.

§ Special Bausch & Lomb Optical Company chart.

If the patient has a very high myopia or a very high hyperopia, one may often be surprised by the amount of near vision obtainable if the reading material is held close to the naked eye. This is an examination which should always be made upon patients falling into these categories: Patients with very high myopia, even with macular lesions, can often read surprisingly well with the naked eye, holding the reading material practically at the nose.

If it is important that the patient have distant vision for use in the theater, for TV, in looking for a bus number, or in some specific employment, such as working at arm's length on a machine, then a telescopic lens will probably be needed. If a satisfactory one can be fitted, the addition of a reading cap may also solve the problem of reading at a more nearly normal distance from the eye than is possible with the average magnifying glass.

A surprisingly high percentage of patients can be made to read with high plus lenses, +5.00, +7.00, +10.00, +15.00, +20.00 D., or even greater. One should start in these cases with a +4.00 or +5.00 lens and then increase by 2 D. at a time until the patient is able to read. It is advisable to use newspapers or magazines here rather than the ordinary Jaeger charts, which are impractical for this purpose. If the patient wants to read a newspaper, that should be the target used. One must be very patient, especially at first, when the subject is actually learning to read again. If he is permitted to take his own time, or even to go out and sit in the waiting room with the plus sphere in the trial frame and "play with it," as it were, it may be found that he will do much better than expected. Frequently the patient who fumbles in the beginning with type as large as Jaeger 7 or so will, as he learns to read, come down to the point where he sees much smaller type with the same lens. If the procedure is repeated, at a later date, the patient may even see the same small type with a weaker sphere. Obviously, the weakest lens that enables the patient to read or to perform the task which he desires is the best prescription for him. Common sense must be used in compiling the final prescription. If, for example, a patient who can read a newspaper with a +10.00 lens requires a +15.00 lens for telephone type, one is better off to give him the +10.00 lens and allow him to use an additional magnifying glass in order to read the telephone book. The importance of illumination should always be explained to the patient.

The simple use of a high plus lens will be adequate for an amazingly large number of patients. A recent experience is a case in point: A 78-year-old physician was seen who stated that he had a cataract and was under the care of a famous ophthalmologist. He was going to return to that man when his cataract was ready for surgery. However, both his ophthalmologist and the latter's assistant had informed him that he could not be given any lens with which to read. This patient was able to read fine type with a +7.00 lens. It was unfortunate he had not been given the benefit of a refraction previously.

Kestenbaum ‖ has suggested that one can observe as a fixed rule that the dioptric power of the plus lens used will be a reciprocal of the vision. That is, if the vision is 20/200, the reciprocal is 10 and a +10.00 lens (2½-power magnification) is indicated. If the vision is 4/200, one would require a 50 D. lens, etc. While the problem is not quite that simple, this rule may be of help. We have seen 2/200 to 3/200 vision helped with a +19.00 lens, and 20/200 vision with numerous scotomata unaided by anything short of the 25-power Megascope, etc.

Persons with less extreme visual loss (say in the 20/50 range) are often aided by simply bringing the reading material closer to their eyes. This takes advantage of the fact that the retinal image is magnified in direct proportion to the proximity within which the object is moved closer to the eye.

Frequently the patient can be handled by a combination of a high plus lens and some

‖ Kestenbaum, A.: Personal communication to the authors.

type of magnifying device. For example, a musician who wanted his glasses only for the purpose of learning his music, so that he could then play from memory, was able to read it with a +16.00 lens. However, with a combination of a +7.00 lens and a Plasta Cataract Reader (which has a magnification of about 5 powers, with a very good field), he was able to read his music more rapidly and comfortably. This combination was given to him and rendered him better able to work efficiently. Many low-vision patients are musicians. They need their glasses mainly for the purpose of learning their music, and not for use while performing. Any lens or combination of lenses which can help them to learn their music will obviously rehabilitate them from the point of view of employment. It may be advantageous in the very extreme cases of this type to have them obtain music which is drawn out already magnified and then to superimpose magnifying devices upon this enlarged music scale.

In the application of magnifying devices, it is important to remember that while the lens magnifies the size of the image of the object viewed, it does not magnify the scotoma. This is the secret behind the success of magnification. The device must render the retinal image larger than the scotoma. In the case of generalized retinal depression, as in optic atrophy, the stimulus provided by the magnifier must be great enough to stimulate the retina to see. It is in the latter group that intense light is extremely important. These patients require a more concentrated light than does the group with macular lesions.

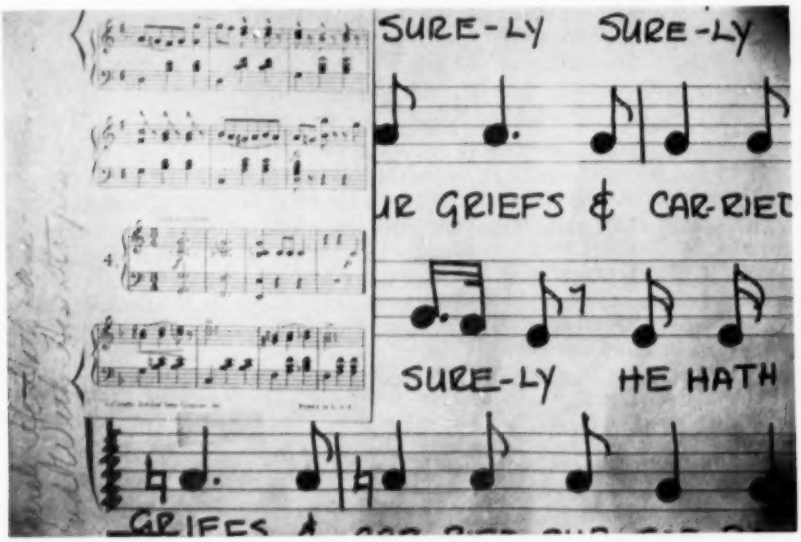

Fig. 5.—Many low-vision patients are musicians. If they cannot be made to read ordinary music sheets, perhaps a friend can draw out the music in larger size, which the patient can then read with the use of magnification. The picture illustrates an ordinary sheet of music which the patient could not be made to read. Her friend drew the music on the scale shown here. With the use of magnification the patient could then study the score.

CONCLUSION

The principles of magnification, as related to low-vision cases, are enumerated. A brief description of the available devices and fields of application is given. It is again stressed that no low-vision patient with measurable Snellen vision should be written off as hopeless until he has been given a good trial with these devices.

An attempt has been made by the authors, singly or together, to discuss this subject with all possible workers in the field. To some extent, many of the statements contained here reflect these opinions. Many of the statements contained in the first part of this paper reflect common knowledge present in the average text on physiologic and physical optics and lenses.

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News and Comment

SOCIETY NEWS

Virginia Society of Ophthalmology and Otolaryngology.—The Virginia Society of Ophthalmology and Otolaryngology will have its annual fall meeting in Richmond at the Baruch Auditorium in the Medical College of Virginia, on Nov. 29 and 30 (Otolaryngology) and on Dec. 1 and 2 (Ophthalmology).

The speakers for the Otolaryngology program are Dr. Victor Alfaro, Dr. Lawrence R. Boies, Dr. Aram Glorig, Dr. Robert J. Huebner, Dr. Lyle M. Sellers, Dr. Ben Senturia, and Dr. Henry L. Williams.

The speakers for the Ophthalmology program are Dr. Howell W. Brown, Dr. James Spencer Dryden, Dr. William M. Hart, Dr. William Howard, Dr. Edward Norton, and Dr. Henry P. Wagener.

For additional information, write Dr. Pastore, chairman, Box 25, M. C. V. Station, 1200 E. Broad St., Richmond 19, Va.

Experimental Tonography in Rabbits

Effect of Unilateral Ligation of Common Carotid Artery on Aqueous Humor Dynamics As Studied by Means of Tonography and Fluorescein Appearance Time

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Clinical tonography, described by Grant [10] in 1950, has proved of value for the study of the mechanism of aqueous flow under physiological and pathological conditions. It is of great help in the diagnosis of glaucoma and in the evaluation of the therapeutic effect of drugs and of surgery in glaucoma. Though the simplifying assumption involved in the interpretation and calculation from the tonographic tracings necessarily introduces some systematic errors, these do not detract appreciably from the value of tonography as a means of exploring problems of aqueous flow.

The purpose of this study was to investigate under experimental conditions one vascular factor which might influence aqueous flow and to see whether tonography in experimental rabbits could be used as an effective tool for the analysis of the effects.

Tonography in rabbits was reported only briefly by Grant.[10] He stated that recordings were made on rabbit eyes in the same manner as on human eyes. He found that in normal rabbits the decline in intraocular pressure during application of the tonometer resembled that in humans, but gave no details.

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From the Wilmer Ophthalmological Institute of The Johns Hopkins University and Hospital.

Presented at the meeting of the Wilmer Residents Association, Baltimore, April 1, 1955.

Hadassah - Rothschild - University (Dr. Kornbluth); University of Uppsala (Dr. Linnér).

This study has been supported in part by a grant from the W. K. Kellogg Foundation and in part by a training grant from the National Institute of Neurological Diseases and Blindness.

We were initially unable to obtain reliable and reproducible tonographic tracings in rabbits with topical anesthesia alone. Consequently, tonography in the present study was performed with the animal under general anesthesia, and in this way satisfactory tracings could be produced. It was understood that general anesthesia might introduce changes in aqueous humor dynamics, but it was felt that valid comparisons between the two eyes of the same animal could nevertheless be obtained.

TECHNIQUE

Pigmented male rabbits weighing between 2 and 3 kg. were used in all experiments.

Tonography.—The animals were anesthetized by intravenous injection of pentobarbital (65 mg/cc.; 0.5 to 0.6 cc/kg.). After instillation of 0.5% Ophthaine (2-diethylaminoethyl-3-amino-4-propoxybenzoate HCl [Squibb], into each conjunctival sac, a nonabsorbable surgical (silk) suture was put through the nictitating membrane and held back by a small clamp. This exposed the whole cornea for placement of the tonometer. The eye, directed downward during the tonographic procedure, was protected from pressure by placing the rabbit's head on a ring-formed towel. In 10 to 15 minutes following the injection of pentobarbital, tonographic tracings were obtained, using a 5.5 gm. plunger weight for a period of four minutes, as described by Grant.[10] In four animals continuous tonographic tracings were taken over a period of 13 to 17 minutes. Tonography was performed first on the right eye and immediately thereafter on the left eye, the tonometer being cleaned thoroughly before examination of each eye. Care had to be taken that the general anesthesia in the animal had reached a level of steady state which was neither too superficial nor too deep. In the former case the appearance of nystagmus interfered with tonography, while in the latter the rolling of the eyes, due to lack of tonus of the external eye muscles, made it very difficult to keep the tonometer on the center of the cornea. The results were calculated

according to the latest tables of Friedenwald,* and ocular rigidity was determined by obtaining readings with 5.5 and 10 gm. plunger weights (Friedenwald[7]). A Müller electronic tonometer connected to a Brown potentiometric recorder was used.

Fluorescein Appearance Time.—The rabbits were given a light general anesthesia by intravenous injection of a smaller amount of pentobarbital (0.3 cc/kg.). The rabbits were fastened to a wooden board with a towel. Two and a half cubic centimeters of a 5% solution of fluorescein (C. F. Kirk) was given intravenously, and the time between the appearance of the dye in the nictitating membrane and in the pupillary area of the anterior chamber was measured. Both eyes were examined simultaneously with separate slip-lamps by separate observers. The method of using the fluorescein appearance time as a measure of the rate of flow of aqueous has been described by Linnér and Friedenwald.† These measurements were made one or two days after carotid ligation.

Ligation of the Common Carotid Artery.—The right common carotid artery was ligated and cut, with the rabbit under general anesthesia and tonography performed thereafter at various periods, ranging from 1 to 10 days. After occlusion of the common carotid artery on one side the animals became more susceptible to the intravenous injection of pentobarbital, and a smaller amount (0.3-0.4 cc/kg.) had to be used for general anesthesia.

One or two days following the occlusion a number of rabbits were given an intraperitoneal injection of 1000 mg. of sodium ascorbate, and 30 minutes later the fluorescein appearance time was measured, followed immediately by tonography. Some rabbits received instead an intravenous injection of 200 mg. of sodium ascorbate in isotonic solution. Ten minutes after the injection the fluorescein appearance time was determined and tonography performed.

The episcleral venous pressure was measured with the rabbit under pentobarbital anesthesia, without a tonometer resting upon the eye, according to the method described by Linnér.[14]

RESULTS

The calculations from tonographic tracings were carried out, using data derived from calibrations on human eyes. It was therefore important to see whether the tables used for tonographic calculations in humans could be applied to the measurements in rabbits. The ocular rigidity was studied in several series of rabbits. The results showed, however, a considerable variation from one group to another.

In one group of rabbits studied together with Dr. E. Prijot, the ocular rigidity was determined in 10 eyes starting with the 5.5 gm. weight, and in another 10 eyes starting with the 10 gm. weight. The average ocular rigidity was found to be 0.0092 in the first group and 0.025 in the second group. Presumably, the difference in those two estimates is attributable in part to a massage effect, and the true value should lie between these extremes. A reasonable estimate for the whole group of 20 eyes, which also was in fair agreement with other measurements, was a value of about 0.015 for the average ocular rigidity.

In four rabbits the tonographic tracings were continued until no further fall in pressure took place, indicating that a steady state had been reached. Under this condition the final intraocular pressure with the tonometer resting on the eye (P_t) should be approximately the same as it was in the undisturbed eye before the tonometer was placed on the cornea (P_o); the aqueous humor is flowing out of the eye at the same rate as it is being formed. It took between 12 and 14 minutes to reach this state. The tonometer was kept on the cornea for another three to four minutes in order to be sure that no further fall in intraocular pressure would take place. There was a fairly good agreement between initial P_o and final P_t (Table 1) when the calibration tables for human eyes were used to estimate the pressure.‡

In 14 eyes the episcleral venous pressure was determined and found to be 8.94±0.17 mm. Hg, which is in good agreement with the value previously found by Seidel.[15]

* Friedenwald.[9] The validity of applying these tables to rabbits is discussed below.

† Linnér, E., and Friedenwald, J. S.: Appearance Time of Fluorescein As an Index of Aqueous Flow, preliminary report presented at the meeting of the Wilmer Residents Association, Baltimore, April 2, 1954.

‡ If K is smaller in rabbits than in man, the estimate of P_o using human calibration tables should be too low. Actual comparison of estimated P_o with the final P_t shows that no large correction in this direction is permissible.

TABLE 1.—*Tonographic Tracings in Rabbits Until Steady State Was Reached*

Initial P_o, Mm. Hg	Final P_t, Mm. Hg
24	22.0
24	23.3
26	24.6
31	28.5

Tonographic measurements were made in 14 normal rabbits (Table 2). The intraocular pressure and the rate of flow of aqueous in the right eye, where the tonography was performed first, was slightly higher than in the left eye. The difference, calculated as the ratio between the right and the left eye, is statistically significant. The coefficient of facility of outflow is the same in the two eyes. No significant correlation between the level of the original intraocular pressure, varying from 37 to 14 mm. Hg, and the coefficient of the facility of outflow was found in 23 rabbit eyes. The second eyes, in which the intraocular pressure could have been influenced by tonography performed on the first eye, were not included in this series.

A phenomenon similar to that found in normal rabbits was observed in normal human subjects (Table 3). After tonography on the first eye the average intraocular pressure in the second eye was found to be significantly lower than in the first eye. On the other hand, no significant difference was found between the coefficient of facility of outflow of the second and that of the first eye. A continuous recording of the diastolic blood pressure during the tonographic procedure of the two eyes did not reveal any consistent changes.

TABLE 2.—*Tonographic Measurements in Fourteen Normal Rabbits**

		Right Eye	Left Eye	R/L
P_o	*m*	23.21	21.36	1.09
	s	5.20	4.86	0.091
	e	1.39	1.30	0.024
C	*m*	0.20	0.30	1.00
	s	0.042	0.040	0.074
	e	0.011	0.011	0.020
F	*m*	4.37	3.82	1.20
	s	1.87	1.97	0.25
	e	0.50	0.53	0.066

* Right eye examined before left eye. P_o = intraocular pressure, in millimeters Hg; *C*, facility of outflow (cu. mm/min/mm. Hg); *F*, flow of aqueous (cu. mm/min.); *m*, arithmetic mean; *s*, standard deviation; *e*, standard error of the mean.

TABLE 3.—*Tonographic Measurements in Sixteen Normal Humans**

		Right Eye	Left Eye	R/L
P_o	*m*	15.04	13.72	0.93
	s	2.60	2.15	0.101
	e	0.65	0.54	0.025
C	*m*	0.19	0.19	0.98
	s	0.032	0.037	0.079
	e	0.0079	0.0093	0.020

* Right eye examined before left eye. P_o = intraocular pressure, in millimeters Hg; *C*, facility of outflow (cu. mm/min/mm. Hg); *m*, arithmetic mean; *s*, standard deviation; *e*, standard error of the mean.

The fluorescein-appearance time measured in seconds in 10 normal rabbits was as follows: right eye, 78.9±5.74; left eye, 82.6±5.70; R/L, 0.95±0.021. There is no significant difference between the two eyes. Tonography was not performed on these eyes prior to the determination of the appearance time.

Tonography was performed on 15 rabbits one to two days following occlusion of the right common carotid artery (Table 4). The intraocular pressure in the right eye is about 3 mm. (15%) lower than that in the left eye. The coefficient of facility of outflow in the right eye is decreased by 25% and the flow of aqueous in the right eye diminished by 45% as compared with the left eye of the

TABLE 4.—*Tonographic Measurements in Fifteen Rabbits, One to Two Days Following Ligation of Right Common Carotid Artery**

		Right Eye	Left Eye	R/L
P_o	*m*	17.33	20.53	0.86
	s	4.07	4.90	0.12
	e	1.05	1.27	0.032
C	*m*	0.22	0.30	0.75
	s	0.035	0.045	0.12
	e	0.0090	0.012	0.031
F	*m*	1.91	3.64	0.55
	s	1.16	2.06	0.18
	e	0.30	0.53	0.046

* P_o = intraocular pressure, in millimeters Hg; *C*, facility of outflow (cu. mm/min/mm. Hg); *F*, flow of aqueous (cu. mm/min.); *m*, arithmetic mean; *s*, standard deviation; *e*, standard error of the mean.

same animal. However, as found in normal rabbits, tonography on one eye lowered the intraocular pressure and the aqueous flow in the second eye. The comparison must therefore be made with the normal eye not influenced by any procedure on the other eye in order to reveal the total effect of carotid ligation. Tonography was always performed first on the right eye. By comparing the right eye after carotid occlusion with the right eye in the normal group, the intraocular pressure and the coefficient of facility of outflow were found to be decreased each by 25% and the aqueous flow to be diminished by 56%. All the above-mentioned differences are statistically significant.

The fluorescein-appearance time, measured in seconds, in nine rabbits one to two days following ligation of the right common carotid was as follows: right eye, 92.3±8.2; left eye, 70.0±7.47; R/L, 1.36±0.087. This difference is statistically significant. Tonography was not performed on these eyes prior to the determination of the appearance time. According to this method, the rate of flow of aqueous in the right eye was diminished by about 30% as compared with the left eye.

Tonographic measurements were made in nine rabbits one to two days following ligation of the right common carotid artery at high ascorbic acid concentration above saturation level (Table 5). The administration of excess ascorbic acid did not give results significantly different from the results obtained in rabbits at physiological ascorbic acid levels (Tables 4 and 5). This is also true for the fluorescein-appearance time measured in five rabbits one to two days following ligation of the right common carotid artery at high ascorbic acid level, which showed a value for the right eye of 65 seconds and for the left eye of 46 seconds, and a ratio of right eye to left eye of 1.42. There was a great variation from animal to animal, and the difference between flow rates at low and high ascorbic acid levels is not statistically significant.

TABLE 5.—*Tonographic Measurements in Nine Rabbits One to Two Days Following Ligation of Right Common Carotid Artery at High Ascorbic Acid Level*[*]

		Right Eye	Left Eye	R/L
	m	15.00	19.80	0.76
P_o	*s*	3.56	3.04	0.16
	e	1.19	1.01	0.052
	m	0.21	0.28	0.75
C	*s*	0.036	0.032	0.13
	e	0.012	0.017	0.042
	m	1.27	2.88	0.44
F	*s*	0.61	0.59	0.22
	e	0.20	0.20	0.072

[*] P_o = intraocular pressure, in millimeters Hg; *C*, facility of outflow (cu. mm/min/mm. Hg); *F*, flow of aqueous (cu. mm/min.); *m*, arithmetic mean; *s*, standard deviation; *e*, standard error of the mean.

TABLE 6.—*Episcleral Venous Pressure in Three Rabbits One Day Following Ligation of Right Common Carotid Artery*

Right Eye, Mm. Hg	Left Eye, Mm. Hg	R/L
10.05	10.15	0.99
9.70	10.35	0.96
8.40	8.80	0.96

The episcleral venous pressure was measured in both eyes of three rabbits one day following ligation of the common carotid artery (Table 6). No significant difference between the two eyes was found.

COMMENT

The first question to be answered when doing tonography on rabbits was whether the tables calculated for pressure and volume relations in human eyes could also be applied with reasonable accuracy for calculations in rabbit eyes.

It was found that the ocular rigidity of rabbit eyes was fairly close to that of human eyes. The tonographic tracings extending to a steady state showed that there was a good agreement between initial P_o and final P_t. P_t values as found by Friedenwald[8] are not significantly different in rabbit and human eyes. It seemed, therefore, justifiable to make calculations from the tonographic tracings in rabbits using the tables compiled for human eyes. Even though a systematic error may be involved, useful information can be obtained by comparing the results of the two eyes of the same animal under various unilateral experimental conditions or by comparing the

same animal before and after an experimental procedure.

The average intraocular pressure in rabbits was about 23 mm. Hg. The episcleral venous pressure was 9 mm. Hg, as compared with 11 mm. in humans. The intraocular pressure in rabbits is higher than that in humans. The outflow pressure in rabbit eyes, therefore, is appreciably higher than that of human eyes (14 mm. Hg in rabbits, as compared with about 5 mm. Hg in humans).

The coefficient of facility of outflow was 0.30 cu. mm/min/mm. Hg. The flow of aqueous as derived from tonography was 4.37 cu.mm/min. This result compares well with the values obtained by Kinsey, Palm, and Cavanaugh,[12] using sodium and thiocyanate as test substances. They found a rate of aqueous flow of 1.7% of the anterior chamber volume per minute. If the volume of the anterior chamber is taken as 250 cu. mm., this rate of aqueous flow would be equivalent to an outflow of 4.25 cu.mm/min. These values are higher than the ones obtained by other authors, applying different methods. Bárány and Kinsey,§ using paraaminohippuric acid, found a flow of 2.7 cu.mm/min. There is, however, some evidence indicating that *p*-aminohippuric acid causes a decrease in the rate of aqueous flow.‖ Bárány,[3] studying the resistance to flow through the angle of the anterior chamber supravitally, measured a facility of only 0.19 cu.mm/min/mm. Hg, which, accordingly, gave a flow of 2.8 cu.mm/min.

After performance of tonography over a period of four minutes on one eye of a rabbit, observations on the other eye revealed a lower intraocular pressure by 9% and a decrease in the rate of aqueous flow by 20%. A similar phenomenon has been observed in human eyes (Table 3).

If a steady state had not been reached in the second eye at the time of tonography, variation in the degree to which the new steady state had been approached would tend to increase the scatter in the estimates of coefficient of facility of outflow. Moreover, individual variations in each rabbit and slight variations in the intervals between tonography in the first and the second eye would tend to produce a larger standard deviation. However, the close agreement between the standard deviations of the coefficients of the facility of outflow in the two eyes permits the conclusion that by the time tonography was started on the second eye that eye had already reached a steady state.

Ligation of the common carotid artery on one side caused a decrease of intraocular pressure, of the coefficient of facility of outflow, and of aqueous flow on the ligated side. This decrease was most marked during the first or second day, and return to normal values occurred gradually over a period of five to seven days. The fall in intraocular pressure on the ligated side amounted to nearly 6 mm. Hg. The intraocular pressure on the nonligated side remained unchanged (Tables 2 and 4). Bárány,[1] using topical anesthesia and tonometry, found a decrease in intraocular pressure of about 4 mm. Hg on the ligated side one day after ligation of the carotid artery.

With regard to our finding of a 25% decrease in the facility of outflow on the ligated side, it might be argued that this decrease could be due to calibration errors in the application of tonography to rabbits, such that an erroneously decreased estimate of the coefficient of facility of outflow would be correlated with lower intraocular pressure. However, observations on a group of normal rabbit eyes did not reveal any correlation between the initial intraocular pressure and the coefficient of facility of outflow. It would, therefore, appear improbable that the observed decrease in the coefficient of facility of outflow on the ligated side was due to calibration errors. The decrease of the coefficient of facility of outflow appears to be a real one. This finding suggests the existence of a homeostatic mechanism for the maintenance

§ Bárány and Kinsey.[6] Kinsey and Bárány.[11]

‖ Friedenwald, J. S.: Ascorbic Acid Turnover in the Aqueous, read at the 17th International Congress of Ophthalmology, New York, 1954.

TABLE 7.*—*Coefficient of Facility of Outflow in cu.mm/min/mm.Hg Measured by Perfusion of Enucleated Rabbit Eyes Following Ligation of Right Common Carotid Artery* †

	Right Eye	Left Eye	R/L
	1-2 Days		
m	0.258	0.228	1.14
s	0.0828	0.0819	0.40
e	0.020	0.021	0.097
n	17	17	17
	3-11 Days		
m	0.252	0.263	0.98
s	0.0655	0.0771	0.176
e	0.0169	0.020	0.046
n	15	15	15

* Peter, P., and Rabaey, M.: Personal communication to the authors.

† Abbreviations are as follows: *m*, arithmetic mean; *s*, standard deviation; *e*, standard error of the mean; *n*, number of eyes.

of a relatively constant intraocular pressure in the face of a changing rate of aqueous flow.

Bárány [3] raised the question "whether changes in the outflow resistance through the trabecular meshwork could occur in the course of the physiological regulation of intraocular pressure." He tried to induce changes in resistance in vivo and attempted to define the factors which influence the barrier in vitro. Among different procedures, Bárány measured the resistance to flow supravitally on enucleated eyes three to six days following unilateral ligation of the common carotid artery. He found a decrease of the coefficient of facility of outflow of about 8% on the ligated side, and this decrease was 2.5 times its standard error.

On the other hand, Peter and Rabaey,¶ who repeated these experiments on enucleated eyes, did not find a significant change in the coefficient of facility of outflow # (Table 7). Bárány had a larger series and a smaller standard deviation than Peter and Rabaey. The change in coefficient of facility of outflow was, however, larger in the living rabbit. The difference between the results in vivo and those in vitro seems, therefore, to indicate that the nature of this outflow change is partly of a physiological nature, disappearing after enucleation.

The rate of aqueous flow as calculated from tonography diminished by about 56%. Using the technique of fluorescein-appearance time, it was found that the rate of aqueous flow on the ligated side was decreased by about 30%. A smaller drop in the rate of aqueous flow on the ligated side was reported by Bárány,[2] and Davson and Matchett,[5] using radioactive sodium as the test substance.

Becker * determined the ascorbic acid concentration in the aqueous humor of the posterior and anterior chamber in 15 rabbits one day following unilateral ligation of the common carotid artery (Table 8). By use of the equation of Kinsey, Palm, and Cavanaugh,[12] the ratio between aqueous outflow and diffusional coefficient was calculated. Assuming that there was no change in the diffusion coefficient of ascorbic acid across the blood-aqueous barrier, Becker * calculated the ratio between the aqueous flow on the ligated and that on the nonligated side. The aqueuos flow was found to be diminished by $27 \pm 4.92\%$ on the ligated side. This decrease was statistically significant.

Linnér [13] had shown a decrease of ascorbic acid concentration in the aqueous humor of the anterior chamber on the ligated side at plasma ascorbic acid levels below saturation, and no such decrease above saturation level. With the above studies in mind, further experiments were carried out to ascertain

* Becker, B.: Personal communication to the authors.

TABLE 8.*—*Ascorbic Acid Concentration in Posterior and Anterior Chamber of Fifteen Rabbits One Day Following Ligation of Right Common Carotid Artery* †

	Nonligated Side		Ligated Side	
	PC	*AC*	*PC*	*AC*
m	34.78	26.43	33.05	22.54
s	7.74	5.65	7.69	4.82
e	2.00	1.45	1.99	1.25

* Becker, B.: Personal communication to the authors.

† Concentration in milligrams of ascorbic acid per 100 ml. *m* indicates arithmetic mean; *s*, standard deviation; *e*, standard error of the mean.

¶ Peter, P., and Rabaey, M.: Personal communication to the authors, 1955.

This work was done at the Wilmer Institute, Johns Hopkins University and Hospital, Baltimore.

whether plasma levels of ascorbic acid above saturation could restore the aqueous flow to a normal rate. No increase of the rate of aqueous flow was found in tonographic examinations on the ligated side, or on the nonligated side (Table 5). The ratio between the rate of flow of aqueous on the ligated and that on the nonligated side as measured by fluorescein-appearance time was also unchanged by addition of ascorbic acid to a level above saturation.

The slower flow of aqueous on the ligated side results in an increased diffusional loss of ascorbic acid. The effect of the increased diffusion on the ascorbic acid concentration in the anterior chamber could be counteracted by an increased concentration of ascorbic acid in the posterior chamber. No change in the concentration of ascorbic acid in the anterior chamber would occur if these two factors were in balance with each other. The previous findings of equal ascorbic acid concentrations in the anterior chamber of the two eyes above saturation level could be explained by assuming that this is the mechanism.

The situation is different below saturation level. There, the rate of plasma flow through the ciliary processes seems to be the limiting factor for the amount of ascorbic acid transferred from plasma to the posterior chamber. Under those circumstances ascorbic acid can be used as a test substance for measuring the plasma flow through the ciliary processes. The amount of ascorbic acid entering the eye can be determined if the aqueous flow and the concentration in the posterior chamber are known. According to Becker (Table 8), no significant difference was found between the concentration of ascorbic acid in the posterior chamber on the ligated and that on the nonligated side. Becker's experiments were performed on animals with normal plasma ascorbic concentrations. Under these circumstances, one can conclude that the amount of ascorbic acid transferred to the posterior chamber on the ligated side is decreased to the same extent as the rate of aqueous flow. Using ascorbic acid as an indicator, the rate of plasma flow through the ciliary processes would be diminished to the same extent as the decrease in aqueous flow one day following ligation of the common carotid artery.

SUMMARY

Tonography was performed on rabbit eyes. The value for the rate of aqueous flow in normal rabbit eyes was in close agreement with determinations using chemical methods. After tonography on one eye, a decrease in the intraocular pressure and the rate of aqueous flow was found in the second eye, but the coefficient of facility of outflow remained unchanged. Unilateral carotid ligation caused a decrease in the rate of aqueous flow, and this decrease was confirmed by the two other, independent, methods. The coefficient of facility of outflow was decreased on the ligated side, suggesting that there exists a homeostatic mechanism for the maintenance of a relatively constant intraocular pressure in the face of a changing rate of aqueous flow.

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News and Comment

GENERAL NEWS

Committee on Ophthalmic Pathology, American Academy of Ophthalmology.—Dr. Michael J. Hogan, chairman of the Committee on Ophthalmic Pathology of the American Academy of Ophthalmology and Otolaryngology, announces that specimens of eyes will be received by the following institutions for processing:

Institution	Number of Additional Eyes Possible to Process Yearly
Baylor University College of Medicine, Houston, Texas	100
Brooklyn Eye and Ear Hospital, Brooklyn	25
Cleveland Clinic Hospital, Cleveland	100
Cornell University Medical Center, New York	25
Doheny Laboratory, St. Vincent's Hospital, Los Angeles	120–150
Emory University School of Medicine, Atlanta	50
Episcopal Eye, Ear, Nose & Throat Hospital, Washington, D. C.	75
Eye, Ear, Nose, and Throat Hospital, Pittsburgh	50–75
Grace-New Haven Community Hospital, New Haven, Conn.	25
Manhattan Eye, Ear and Throat Hospital, New York	25
Medical College of Alabama, Birmingham, Ala.	50
Medical College of Virginia, Richmond, Va.	15
Montefiore Hospital, New York	50
Northwestern University Medical School, Chicago	50
Ohio State University College of Medicine, Columbus, Ohio	100
St. Mary's Group of Hospitals, St. Louis	80-100
Stanford University Hospitals, San Francisco	200
State University of Iowa College of Medicine, Iowa City	5
Tulane University of Louisiana School of Medicine, New Orleans	50
University of California Medical School, Department of Ophthalmology, San Francisco	200
University of Cincinnati College of Medicine, Cincinnati	100
University of Colorado School of Medicine, Denver	50
University of Kansas School of Medicine, Kansas City	50
University of Oklahoma School of Medicine, Oklahoma City	100
University of Oregon Medical School, Portland, Ore.	50
University of Pennsylvania Hospital, Philadelphia	50
Washington University School of Medicine, St. Louis	75–100
Wayne University Kresge Foundation, Detroit	100

Rate of Sterilization as a Factor in the Selection of Ophthalmic Solutions

Experimental Studies with a Proposed Method of Preparing Sterile Solutions

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In the past decade many bacteriological studies have been pursued on an in vitro scale in an attempt to evaluate activity of proposed ophthalmic preservatives. These included the work of McPherson and Wood [1]; Skolaut [2]; Scigliano and Skolaut [3]; Krause, Dauer, and Guth [4]; Heller and associates,[5] and Murphy, Allen, and Mangiarcine.[6] It is apparent from these studies that many of the authors consider bacteriostatic concentrations to be a safe level of preservation for these solutions. Murphy, Allen, and Mangiarcine directly stated that bacteriostatic and fungistatic powers were among the properties to be possessed by an ideal ophthalmic preservative. More recently, Lawrence [7] has published a general review of chemical preservatives for ophthalmic solutions. He concludes:

> A careful review of the literature reveals that in preparing and dispensing ophthalmic drugs, chlorobutanol, phenylmercuric nitrate, and benzalkonium chloride are considered the bacteriostatic agents most suitable for providing "self-sterilizing" solutions.

The concept that bacteriostatic concentration levels present adequate preservation for ophthalmic solutions appears to be a generally accepted view. It is, indeed, the level of preservation found in proprietary ophthalmic preparations. We contend, however, that bacteriostatic concentration levels present an inadequate margin of safety when the ophthalmic solution is used by the physician in his office, emergency treatment room, clinic, surgery, or hospital ward. The point of disagreement rests critically on a consideration of the time period of exposure required to sterilize the solution.

Price [8] has reviewed the experimental and scientific meaning of the terms bacteriostatic, bactericidal effect, and rate of disinfection. For each bacterium, between the time of first contact with the disinfectant and the time of death, there is a period of inhibition. The cause, nature, and degree of inhibition differ with the disinfectant applied, but the response may be called bacteriostasis. When one deals with a large group of test organisms, in which there is a wide range of susceptibility and resistance, the concept of bacteriostasis as applied to the whole group becomes less meaningful. The experiments of Price confirm the finding that inhibition and killing go hand-in-hand, until sterilization finally occurs. In this respect the quotation from the Lawrence review is entirely correct; that is, if bacteriostatic concentrations of chlorobutanol, phenylmercuric nitrate, or benzalkonium chloride are in contact with a susceptible bacterial population for a sufficient length of time, they may produce a sterile solution.

Furthermore, it must be emphasized that experimental data are valid only under the particular set of conditions established. This is particularly true with in vitro tests, in which a variation in these conditions might bring about revival of a presumable "dead"

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bacterial cell or, at least, a restoration of some of its biological functions. An unambiguous procedure must be available for the elimination of the activity of a preservative agent which has been absorbed on the bacteria or carried over in the dilution process. When the trace amounts of chemical preservative go unneutralized in the culturing procedure, their killing action continues during the incubation period, and in many instances the cultures become negative. A false sense of security is the result. In order safely to use bacteriostatic preservative concentrations in ophthalmic solutions, one should know the time period required to sterilize the solution after contamination. Ideally, the data should be obtained from in vitro and in vivo experiments.

During the treatment of the relatively large numbers of patients seen each day by the physician and nurses, one patient with any eye grossly contaminated with Pseudomonas organisms could be the source of a number of infected solutions. Since Pseudomonas aeruginosa is a common inhabitant of human skin, the contaminating bacteria could come from the physician, the nurse, or the patient. It can also be an air contaminant. A freshly opened sterile ophthalmic solution, whether proprietary or compounded, thereby can become a dangerous liability.

Soon after this contamination, the physician very likely may see a patient with an abraded cornea, and he may use one of the contaminated solutions. After the brief exposure to the antibacterial agents, the contaminating bacteria conceivably can and do find their way into the corneal stroma. Once in the corneal stroma, the residual traces of bacterial agents are neutralized by tissue components, and the organisms find an excellent culture medium for rapid growth and dissemination throughout the cornea and the anterior segment of the eye.

In the past 18 months at least eight verified cases of corneal ulceration due to P. aeruginosa have occurred in the San Francisco Bay area. In four other instances groups of solutions contaminated with the same organism have been discovered and removed from active ophthalmic use. In a previous report on 50 samples of fluorescein solution obtained in the San Francisco Bay area from a number of ophthalmologists and other sources, Vaughan[9] found that 54% were contaminated, mostly with Gram-negative rods. Six solutions (12%) contained P. aeruginosa.

EXPERIMENTAL STUDY

Laboratory experiments were conducted on the basic premise that a laboratory in vivo test method could serve as a valuable means of evaluation of sterility. While the ideal in vitro test might detect a single living bacterium, an in vitro test procedure utilizing a poor chemical antagonist might be falsely interpreted as being sterile. Experimental infections of P. aeruginosa in rabbit eyes can be established in nearly 100% of inoculated eyes, with low numbers of bacteria, and produce a fulminating type of infection. By paralleling the in vivo rabbit test procedure with an in vitro bactericidal test procedure, a clarification of the sterilizing potentialities might be achieved. Especially important to the ultimate application of the solution in ophthalmic practice, the rabbit test procedure could contribute information on the relative rate of activity of the antibacterial agents and also clarify the question whether bacteriostatic concentrations are adequate safeguards against potential ocular infections.

MATERIALS

All chemicals utilized met official standards of purity and were prepared from sterile distilled water and reagent buffer chemicals.

Phenylmercuric nitrate, benzalkonium chloride, chlorobutanol, phenylethyl alcohol, and polymyxin B sulfate were tested in buffered or in isotonic saline solutions.

P. aeruginosa strains tested in this study were from human ocular infections. The testing media specified below were prepared according to recognized procedures and concentrations.

METHODS

General Bacterial Test Procedure.—A 1 cc. quantity of a 24- or 48-hour broth culture of P

aeruginosa (approximately 10^9 bacteria) was added to 9 cc. of sterile saline solution of the bacterial agent being tested. In order to evaluate the effect of the bacterial population, dilutions of the original culture were made to counts as low as 1000 bacteria per cubic centimeter. The bacteria were exposed to the test solution for periods varying from five minutes to as long as one week. Various neutralizing procedures were attempted to destroy the action of the antibacterial agent without reducing the viability of the organisms. These included dilution through broth, as well as the various chemical antagonists reported by Lawrence,[10] Klarmann,[11] and Bliss and Warth.[12]

In Vivo Procedures.—Approximately 0.01 cc. of the Pseudomonas-contaminated antibacterial solution was injected at various time intervals intracorneally into two or more rabbit eyes. Studies of the effect of dilution of the original contaminated solution with sterile broth or with the inactivating agent were also undertaken. In one experiment chorioallantoic chick membranes were inoculated as a possible in vivo test method. Periodically, corneal swabs were taken of the infected animals in order to recover and identify organisms from the infected area. Over 300 rabbit eyes were utilized.

In Vitro Bacteriological Procedures.—A number of different media and procedures were investigated. These included the use of nutrient broth, serum-fortified nutrient broth, thioglycollate broth, Avery's broth, and thioglycollate-lecithin-polysorbate 80 (Tween 80) broth. Among solid media tested were plain agar, blood agar, heart infusion agar, and, finally, lecithin (0.5%) in heart infusion agar.

Varying amounts of the P.-aeruginosa-contaminated antibacterial solution up to 1 cc. were added to 9 cc. of the culture medium. Tenfold serial dilutions were done through at least four tubes.

The following procedure of evaluating bacteriostasis was adopted. One cubic centimeter of a sterile solution of the preservative being tested was serially (1:9) diluted through three more sterile broth tubes. The 24- or 48-hour P. aeruginosa culture was diluted to a range of 10^5 to 10^3 bacteria per cubic centimeter. These were added to a set of the preservative-containing broth tubes. Three sets were prepared at varying levels of bacterial count. This procedure was used on the assumption that the dilution of the preservative into the broth tube prior to contact with the bacteria will eliminate the bactericidal activity of the agent. The bacteria will, therefore, be added to a bacteriostatic or an inactive concentration of the preservative. If the culture medium is adequate in neutralizing the bacteriostatic action, the bacteria will multiply.

Stability Test on Polymyxin B Sulfate.—Since the stability of polymyxin alone or in combination with other preservatives is not known, an attempt was made to gain evidence of the stability of the agent under autoclaving temperatures (115 C).

A procedure was developed utilizing the minimum inhibitory concentration test of Finland and associates[13]; polymyxin B sulfate in various ophthalmic vehicles were prepared in quadruplicate by sterile procedures. The vehicles included isotonic saline, 2% boric acid—plain and with 0.1% sodium sulfite—and modified Sorensen phosphate buffer (pH 6.8). Polymyxin B (1000 units per cubic centimeter)* was added to one pair of solutions and both polymyxin (1000 units per cubic centimeter) and benzalkonium chloride (1:10,000) were added to the other pair. One representative from each pair of solutions was autoclaved at 10 lb. of pressure for periods of from 10 to 30 minutes. Both the autoclaved and the unautoclaved solutions were then diluted through a sequence of concentrations with sterile agar. Three strains of P. aeruginosa were streaked on each plate, and the plates were observed for growth for several days.

Results

The results of the in vivo and in vitro procedures are summarized in the Table. While the studies ultimately led to identical end-points in both the in vitro and the in vivo experiments, a great deal of effort was expended in searching for the proper in vitro media and neutralizing conditions, which are reported in detail elsewhere.[14] In the majority of the parallel tests, the in vitro cultures were negative, while corneal ulcerations consistently developed in the rabbits, and P. aeroginosa organisms could be recovered from the corneas.

Pseudomonas-contaminated phenylmercuric nitrate solutions up to 1:10,000 concentration, when subcultured into thioglycollate broth, resulted in sterile plates after one hour's exposure. However, corneal ulcers resulted even after one week's exposure. The use of the proper medium, lecithin-polysorbate 80-thioglycollate broth, eliminated this discrepancy between the in vitro and the in vivo results.

* Ten thousand units of polymyxin B sulfate is equivalent to 1 mg. of the standard polymyxin B sulfate. Since inert ingredients are allowed in the system, 10,000 units does not weigh 1 mg. To avoid confusion, unit values were used in this report.

Benzalkonium chloride, unless properly neutralized, appeared to sterilize a contaminated solution after 5 minutes' contact, while chlorobutanol took less than 60 minutes. Both these compounds were studied until concordant in vitro and in vivo data were obtained with the media reported in the Table.

Study of the results obtained with polymyxin B sulfate confirms the remarkable dependence of the results on the test procedure. Bliss and Warth [12] have previously shown that lecithin was an effective chemical antagonist for polymyxin B sulfate when evaluated against Escherichia coli organisms. adequate system to antagonize the carryover activity of the polymyxin B. One cubic centimeter of the contaminated solution was diluted with 9 cc. of sterile agar at five-minute intervals. Colonies were detected in the agar plates up to 15 minutes' exposure. Intracorneal injection of these contaminated polymyxin solutions (1000 units per cubic centimeter) resulted consistently in infections up to 15 minutes' exposure. No infection resulted after 30 or 60 minutes' exposure.

Since polymyxin B (1000 units per cubic centimeter) was shown clearly to be the chemical preservative of choice against the

Bacteriological Test Data

Antibacterial Agent	Concentration	Longest Exposure Producing Infections*	Sterilizing Time†	Recommended in Vitro Culture Media
Phenylmercuric nitrate	Up to 1:10,000	1 wk.‡	?	Lecithin-polysorbate 80-thioglycollate broth
Benzalkonium chloride	Up to 1:5,000	1-3 days	Greater than 3 days §	Lecithin-polysorbate 80-thioglycollate broth
Phenylethyl alcohol	0.5%-2.0%	8 hr.‡	?	?
Chlorobutanol	0.5% to 0.8%	4-6 hr.	8 (?) to 24 hr.	Lecithin-polysorbate 80-thioglycollate broth
Polymyxin B sulfate	Up to 1,000 units/cc.	15 min.	30 min.	Lecithin (0.5%) in heart infusion agar

* The antibacterial agent was contaminated with a heavy inoculum of a P. aeruginosa strain. After varying time periods, a portion of the solution was injected intracorneally into rabbits. Corneal ulcers developed if viable bacteria were present.

† Evaluated as the shortest time interval which resulted in negative in vivo and in vitro tests.

‡ Longest time period tested.

§ P. aeruginosa bacteria have been deterred in 1:500 solutions of benzalkonium chloride instrument-sterilizing solution in clinic use. After several weeks the bacteria were still detectable, and in one occasion were multiplying.

The addition of polysorbate 80 to the test medium in this instance produced a combination which failed to antagonize the activity of the polymyxin. Our studies confirmed these observations with P. aeruginosa organisms. Utilizing the bacteriostatic test procedure given above, a minimum inhibitory concentration of polymyxin B for our P. aeruginosa strain was found to be above 1 unit per cubic centimeter. However, when contaminated solutions were tested at five-minute intervals in the same media, all the cultures were negative. When 0.5% lecithin (no polysorbate 80) in nutrient broth was used as the diluting medium, negative cultures and subcultures also were obtained.

Ultimately it was found that the use of 0.5% lecithin in heart infusion agar was an P. aeruginosa strains tested, stability tests were conducted as described above. The bacterial culture plates of the autoclaved phosphate solutions showed growth at all dilutions, indicating nearly complete destruction of the active polymyxin moiety. All other formulations showed a small loss of activity but still indicated a minimum inhibitory concentration of 40 units per cubic centimeter or less. This was approximately twice the concentration required in the analogous unautoclaved solutions. One might assume approximately 50% destruction. No difference was noted when both benzalkonium chloride and polymyxin B sulfate were combined. It has been previously reported that citrate and phosphate buffers are somewhat less stable than other buffer

systems.[15] However, even isotonic saline solutions of polymyxin showed deterioration on autoclaving.

COMMENT

In both the in vivo and the in vitro work, our results are in marked disagreement with the studies reported by other workers. As is abundantly apparent from these earlier reports, most of the agents tested appear to possess germicidal activity after sufficient time of contact. Yet they differ strikingly in their rate of germicidal activity. Only a small number of viable organisms are required to produce an infection when injected intracorneally into rabbit eyes. One may wonder whether low concentrations of preservative, usually present in ophthalmic solutions, have had sufficient length of time of exposure to a contamination to sterilize the solution. Certainly, a hazard exists in the office, the emergency treatment room, the clinic, the hospital ward, and the surgery, where a physician or a nurse may treat many patients daily who have corneal wounds or openly infected eyes. The search for a more rapidly acting preservative is essential to the ultimate safety of the patient and the welfare of the physician. The eye physician must be given the opportunity to use liquid medication with complete confidence.

While it was fortunate that we have undertaken the rabbit corneal test, it must be emphasized that we are not proposing that the cornea is a more sensitive test environment than the test tube. An in vitro method, entirely eliminating the effect of the antibacterial agent, may be expected to show greater sensitivity than these rabbit tests. The rabbit tests are useful as a safety precaution in evaluating the relative sensitivity of the in vitro method and have led to some valuable conclusions concerning the preservatives tested.

Phenylmercuric nitrate may not be used in concentration greater than 1:10,000 in ophthalmic solutions, since the presence of halide ions would result in a precipitation of the insoluble phenylmercuric halide. Since the solutions up to this concentration showed growth of the test organism up to one week, we must conclude that this compound when used alone possesses an insufficient rate of bactericidal activity against P. aeruginosa for use in many, if not all, ophthalmic applications.

Benzalkonium chloride was restricted to concentrations below 1:5000, since chronic use of such solutions is irritating to the eye. In one of our test procedures, this concentration was found not only lacking in bactericidal activity after 24 hours' contact but also completely lacking in bacteriostatic activity. The bacteria began multiplying and produced the green pigment common to this species. On the average, more than one day's contact was required to sterilize the solutions with the strains tested. Since a solution may be contaminated and used on several different patients during one day, benzalkonium chloride by itself appears to possess an insufficient rate of kill of the test organisms.

Similarly, we can conclude that chlorobutanol would appear to be ineffective, since positive cultures were found up to four to six hours after contamination. However, when smaller numbers of bacteria were introduced into the system, sterile solutions were found in one to two hours. There is no doubt that chlorobutanol possesses activity under proper conditions of handling. However, the compound is volatile and may be lost during the usual heating period utilized to bring it into rapid solution.[16] Being an organic halide, it spontaneously hydrolyzes in solution, particularly in the alkaline pH, but also in the acidic solution after longer periods of time or upon autoclaving. From these considerations, and from the availability of a more active agent (polymyxin B), we can conclude that the compound is not the agent of choice in the preservation of ophthalmic solutions.

Since polymyxin B (1000 units per cubic centimeter) consistently sterilized heavily contaminated solutions in less than 30 minutes, this agent appears to be the preservative of choice. Yet, as it is not a broad-spectrum bactericide, additional antibacterial

agents must be incorporated to overcome its lack of activity against Gram-positive organisms. The rapid action of benzalkonium chloride against Gram-positive organisms, as well as its compatibility with polymyxin, makes a combination of these agents a logical one in the absence of precipitation reactions or other incompatibilities.

Polymyxin has been reported to be ineffective against certain strains of P. aeruginosa in clinical use. However, the suggested application is essentially in vitro in character, since the antibacterial action takes place entirely in the bottle. Finland and associates[17] tested over 100 strains of P. aeruginosa from human sources and found that all but one was inhibited by 65 units per cubic centimeter. The resistant strain was inhibited by 125 units per cubic centimeter. The studies of Altemeier† on 200 human strains resulted in identical conclusions. At present there appears to be no agent more active against P. aeruginosa strains than polymyxin B sulfate from the perspective of the number of strains involved or in terms of the rate of action.

The results of the stability studies conducted on polymyxin B sulfate alone or in combination with benzalkonium chloride indicate that some of the compound is destroyed during the usual autoclaving procedures. Fortunately, polymyxin is available in a sterile form, and it can be added to a sterile prescription vehicle by aseptic techniques, as will be described later. The addition of 1000 units per cubic centimeter would result in raw material costs of approximately 15¢ per fluidounce over present methods. Polymyxin is stable at room temperature for relatively long times, extending through the period in which the physician would normally use a single prescription (two to three months).

A solution containing benzalkonium chloride, 1 : 10,000, and polymyxin B sulfate, 1000 units per cubic centimeter, is not without certain liabilities from the total perspective of potential contamination. This combination is effective against Gram-positive and many forms of Gram-negative organisms; however, it may not possess effective germicidal action for Proteus organisms. Any antibacterial action against Proteus will rest on the activity of benzalkonium chloride. We do not know the potential effect of this combination against viral or fungal contamination in ophthalmic solutions. Although quaternary compounds, such as benzalkonium chloride, are active against fungi, little is known of the antiviral properties of the mixture. This facet deserves investigation.

We recognize that benzalkonium chloride is incompatible with certain anions, such as nitrate, salicylate, fluorescein, and the sulfonamides.[7] The pharmacist can select the pharmacologically identical pilocarpine hydrochloride or physostigmine hydrochloride in place of pilocarpine nitrate or physostigmine salicylate. These salts would be compatible with the preservation combination. If solutions of sodium fluorescein or sodium sulfonamide are to be compounded by the pharmacist, benzalkonium chloride should not be used. In these cases phenylmercuric nitrate (1 : 25,000) or sodium merthiolate (1 : 50,000) may be used, it being admitted that they are not rapidly acting bactericides, even against Gram-positive organisms. Other bactericides can be suggested for use in the combination, but no equivalent substitute exists for the polymyxin.

The routine use of polymyxin B sulfate need have no deteriorating effect on its employment in therapeutic concentrations in the treatment of acute infections. In these instances, overwhelmingly higher concentrations have been used. The lower concentration found in the prescriptions is not expected to result in resistant strains. In vitro applications, such as that under discussion, may be examined in the light of the work of Finland[17] and Altemeier,‡ who found no resistant strains in their in vitro studies.

A suggested detailed procedure of preparing sterile ophthalmic solutions is being pub-

† Altemeier, W. A.: Personal communication cited by Searle.[14]

‡ Altemeier, W. A.: Personal communication cited by Searle.[14]

lished by us in the pharmaceutical literature.[18] The following is an abstract of the recommended procedure:

1. A stock of sterile ophthalmic vehicles in 8 oz. prescription bottles is prepared.

   Two hundred cubic centimeters of the vehicle (including the benzalkonium chloride, 1:10,000, or other adequate Gram-positive preservative) is added prior to sterilization. After sterilization by autoclaving,§ and just prior to use, the contents of a sterile vial containing 200,000 units of polymyxin B sulfate are added to the vehicles by sterile transfer technique.

2. Ophthalmic dropper bottles are precalibrated and sterilized, as is other required glassware, and kept in stock.

3. The solution is compounded by a simple aseptic transfer.

   The required ophthalmic drugs are weighed, transferred into the sterile, precalibrated prescription bottles, and diluted to volume with the proper isotonic sterile vehicle. The tonicity value of the combination of the drug and vehicle, in nearly all cases, falls within the range which produces no pain and is physiologically safe.

4. If desired, the solution can be filtered through a bacterial retentive membrane as a further precaution.

   This may be done with a syringe and the proper filter adapter and filter membrane. (See Reference 19 for further details.)

5. To restrict any potential hazards in the use of ophthalmic solutions in the office, clinic, or hospital, the use of a disposable dropper is recommended.

   One useful type can be made from ordinary cellophane drinking straws, which are cut in half and autoclaved (15 lb. and 15 minutes) in wrapped packages or wide-mouthed glass containers. A number of these sterile straws may be transferred to a small metal tray for brief periods during the day. The tray would be opened only briefly during the visit of each patient, at which time a forceps can be used to pick up the individual sterile straws.

6. In the special case of sodium fluorescein, the use of the Kimura papers is recommended.[19]

It is apparent from prescription records that the physician has turned to the use of proprietary ophthalmic solutions for both home and office use, presuming that these solutions would possess greater safety than compounded solutions. Prepacked proprietary medication contains only bacteriostatic concentrations of antibacterial agents or slowly acting mixtures. Contamination of these proprietary solutions during use would give no more assurance of safety than a similar compounded solution. It is a trend worthy of serious consideration that we now find miotics, mydriatics, and other generally available drugs being prescribed by the physician in proprietary formulations. This lack of confidence in the practicing pharmacist is unwarranted and dangerous. If the average pharmacist loses the art of proper compounding of ophthalmic prescriptions, the patient and the physician would both pay the burden of inconvenience, while the physician could lose control of the medication available to him.

§ An adequate pressure cooker is available for $25.

SUMMARY AND CONCLUSIONS

The rate of germicidal activity of many commonly used chemical preservatives has been found to be inadequate to maintain sterility of an ophthalmic solution against accidental Pseudomonas aeruginosa contamination.

It is postulated that previous authors have based their conclusions on in vitro techniques which were deficient in procedures required to neutralize the entire action of the test preservative. Both in the in vivo rabbit corneal results and the in vitro data presented here are in marked disagreement with these earlier reports.

Polymyxin B sulfate (1000 units per cubic centimeter) was shown to be the most rapidly acting chemical preservative tested. A combination of polymyxin B sulfate and benzalkonium chloride 1:10,000 appears to possess a broad spectrum and is rapidly bactericidal.

While not having an adequate rate of action for many ophthalmic uses, chlorobutanol (0.5%) was found to be the second choice as preservative.

The stability of polymyxin B and its combination with benzalkonium chloride was investigated, and the results are reported.

A practical method is presented by which the practicing pharmacist can prepare sterile, rapidly germicidal ophthalmic solutions competitive with, or superior to, some of the presently available proprietary products.

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Ocular Prosthetics

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The literature of every race stresses the ability of a person to look another in the eye. Ophthalmologists are aware of the fear that a patient has of being conspicuous by this inability. Withdrawal and personality changes may occur in patients who, because of strabismus or loss of an eye, find it difficult to face the world. Self-confidence usually returns with a successful muscle operation or the fitting of a prosthetic eye. Even before World War II there were approximately 600,000 persons in the United States who wore artificial eyes. Since World War II and the Korean conflict the numbers wearing artificial eyes have increased enormously. The magnitude of the need, therefore, warrants some recommendations for surgery, postoperative care, and fitting of functional and cosmetic protheses.

This presentation is not concerned with specific surgical procedures, nor is it intended as a comprehensive discussion; rather, it is offered as an outline of the practical possibilities and the preferences as we see them after experience with more than 600 selected cases of prosthetic eyes. Only three specific cases are reported from our series by way of examples.

CLASSIFICATION OF OCULAR PROTHESES

The most obvious division of artificial eyes is into two groups: glass eyes and plastic eyes. We are concerned here only with those prosthetic eyes made of plastic. The most complete published classification is by Galeski.[1] Revision has been inevitable with newer materials and manufacturing techniques. Types of ocular prostheses (Fig. 4*A*, *B*, *C*) are herewith presented.

1. *The Snellen Conventional Re-Form Eye.*—The Snellen re-form eye is a frequently used prosthesis, having a horizontal dimension approximately 10% greater than the vertical dimension. The point of greatest vertical dimension is slightly temporal to the center of the pupil. The anterior convex surface has a radius of 12 to 16 mm. The posterior surface is concave. Thickness is about 8 mm. at the cornea and 2 to 3 mm. at the periphery.

2. *Conventional Shell Type.*—The conventional shell type is similar to the conventional, or Snellen, re-form eye but is constructed so that the thickness of the scleral portion is about 1 to 1.5 mm. and is slightly thicker over the corneal portion. This type is indicated when a prothesis is fitted over a phthisical eye or a protruding buried implant, and in cases in which the orbital tissues are protuberant and leave little room for a reform between the tissues and the lids.

3. *Cosmetic Contact Shell.*—The cosmetic contact shell is similar to the first two types but is only 0.5 to 1 mm. in thickness at the cornea. The iris can be aligned to match the normal eye, regardless of exotropia or esotropia of the eye to be fitted. These are fitted only on prescription by an ophthalmologist and are worn like scleral contact lenses. The indication for this appliance is cosmetic correction of any disfigured eye, whether traumatic or otherwise.

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4. *Corrected Cosmetic Contact Shell.*—The corrected cosmetic contact shell is similar to a cosmetic contact shell except that the pupillary space is left clear in order that the patient's optical correction or pinhole may be ground into the central lenticular portion. Excellent results are achieved in cases of albinism, aniridia, photophobia, and irregular iridectomy.

5. *Semishell.*—Half of the semishell prosthesis is a conventional re-form type; the other half is a conventional shell with a gradual transition in thickness between the two portions. These are used when one fornix is normal and the other is too thin or shallow to retain a conventional prosthesis.

6. *Hook or Shelf Type.*—The hook or shelf type of prosthesis is a conventional re-form eye with a hook or shelf at the top, extending back at an angle of approximately 90 degrees. It is indicated in cases of a poor socket and a shallow lower lid which cannot properly retain any other type of prosthesis.

7. *Curl-Back Shell.*—The curl-back shell is somewhat similar to the hook or shelf type in that the upper portion extends back at a right angle, or nearly a right angle, to the vertical chord of the eye. The inferior portion turns downward and backward at an angle of about 135 degrees. These artificial eyes are indicated in cases of shallow or deficient inferior fornices.

8. *Forty-Five-Degree-Bend Re-Form.*—The 45-degree-bend re-form offers conventional re-form eyes with the upper temporal portion bent backward at an angle of 45 degrees from the horizontal. These prosthetic eyes are indicated when an ordinary re-form eye would lean back. The bend prevents a drooping of the temporal portion of the upper eyelid.

9. *Peanut Eye.*—The peanut eye is a conventional re-form shortened in vertical dimension and elongated horizontally with a temporal curve. Peanut eyes are used when a convention re-form eye tends to sink back temporally and pull away from the inner canthus.

10. *Reverse Shape.*—The reverse-shape prosthesis is a conventional re-form eye with the vertical dimension greater nasally and the temporal portion narrower. It is used when the prosthesis has a tendency to rotate in the socket.

11. *Front Build-Up.*—The front build-up is a conventional re-form eye built up at the upper scleral periphery and is used to prevent drooping lids or to obturate a sulcus.

CHOICE OF IMPLANT

Sphere as Anatomic Replacement.—The simple glass sphere was the implant used in over 85% of the 600 cases in our series. In our experience the sphere is the most anatomic type of replacement of the globe from the standpoint of preservation of the surrounding muscles and tissues. When the enucleation is performed, the spherical organ should be replaced by a sphere of inert material: glass, gold, ivory, plastic, bone, tantalum, or other inert material. Glass is used routinely at the Cook County Hospital.

A proper-sized sphere presents no corners, no rough edges, no pressure points, or any friction points—any and all of which conditions cause tissue necrosis, suppuration, and, finally, extrusion, as happens in other types of implants. The sphere, moreover, is by far the least expensive of the implants, from the standpoint of both the implant itself and the cost of the prosthesis to be fitted over it.* The Mules sphere meets all the requirements mentioned.

Prevention of Complications.—From the surgeon's point of view, the operation is relatively simple. The complications encountered, except for possible secretion, in integrated postenucleation implants are rare when spheres are used. The possible complications, as listed by Stone,[18] are (1) secretion, to which should be added infections; (2) granulation tissue or polyps at the conjunctival edge; (3) exposure of the meshwork, and (4) operative difficulties

* References 3, 7, and 9.

with secondary or delayed implants. Another complication which should be mentioned is exposure of the periphery of the prosthesis in extreme nasal and lateral excursions.

Infection and secretion are probably the results of impeded lacrimal drainage and the existence of dead space or diverticula in the cul-de-sacs. With a properly chosen sphere and a properly fitted prosthesis, dead space is virtually eliminated. If the principles of proper fitting of the prosthesis have been applied, the lower puncta will fall against the globe, and drainage will be adequate. Hygienic care of the socket is simple and does not require prolonged postoperative application of antibiotic ointments and complicated routines for care of the prosthesis. The patient himself can remove the prosthesis at any time with little difficulty.

Several other types of implant, including the integrated type, will give more motility,[13] but the potential for pressure necrosis, extrusion, and infection and the necessity for hygienic care are so much greater as to be disadvantageous.

Size.—The diameter of the spherical implant should be about 25% smaller than that of the globe that it replaces. In other words, a sphere about 18 mm. in diameter may be used to replace a globe 24 mm. in diameter. The smaller size favors closure of the conjunctiva without tension, but it should not be so small as to fall backward within the muscle cone, thus giving the appearance of a recessed eye, or perhaps causing a deepening of the superior orbital sulcus. Sugar [14] has devised an operation to obturate a sulcus by insertion of an acrylic implant in the sulcus.

An implant that is too large invites extrusion from tension on the sutures or displacement posteriorly through the opening in Tenon's capsule made by sectioning the nerve. A proper-sized implant will maintain the convexity of the conjunctival surface that will face the prosthesis. It should be firm, but not too firm. It is well to have various-sized sterile spheres on the instrument tray, so that an appropriate sphere is always available. Spheres may be successively inserted and removed until the proper size is found.

MOTILITY

It has been our experience that the best functional and cosmetic results have been obtained when the natural device has been faithfully reproduced—in other words, when a spherical implant has been used prior to fitting ocular prosthesis in cases of enucleation or evisceration.

It is comparatively simple for the prosthetist to fit an appliance over a shrunken or phthisical eye, for the spherical implant corresponds to the globe. Some surgeons perform muscle operations on the shrunken or phthisical eye before fitting a prosthetic shell in the belief that this secures maximum motility in the various positions of gaze without the appearance of exotropia or esotropia. To a large degree, motility obtained is limited by the depth of the fornices and the amount of conjunctiva preserved. This is analogous to the sliding doors on an astronomical observatory. The doors can move only so far as there is space for them to move in; thus, the maximum degree of motility is obtained by tissue preservation.

In cases of traumatized eyes, the maximum degree of motility is obtained when a thin-shell prosthesis, similar to a contact lens, is fitted over the eye. If the shell is made to cover the cornea and only a small portion of the sclera, the prosthesis being deficient at the periphery, there will be no restriction of motility; however, if the prosthesis were extended to the fornices, the motility of the prosthesis would be limited by the depth of the fornices. The eye itself can continue to move back and forth under the prosthesis, and thereby cause an irritation, unless there is clearance between the prosthesis and the cornea.

Examination of the socket a month after operation will reveal a surprising degree of motility of the implant; nevertheless, after a prosthesis is fitted over it, there may be a limitation of motion, because the periphery

of the prosthesis may reach the depth of the cul-de-sac.

Certain types of buried muscle cone implants, such as the hemispherical type of implant with a flat anterior surface, in which the muscles are sutured together through tunnels (Allen type implant [4]), may at first give a greater degree of motility; however, implants of that type may cause other problems, such as pressure necrosis, drooping of the lower lids, or infection.

SURGICAL RECOMMENDATIONS

1. As in all good surgical practice, the procedure for enucleation or evisceration should be carried out as atraumatically as possible and with meticulous care in dissecting away the various planes of cleavage. The more traumatic the operation, the greater the postoperative edema and the more scarring and adhesions that will ensue; consequently, the surgical end-result will make the technician's task more difficult and may give a poor cosmetic effect.

2. An important surgical requisite to satisfactory final fitting of an ocular prosthesis is the preservation of as much conjunctiva as possible.

3. In traumatic cases,[5] even before the decision to enucleate an eye, extreme care is required in repairing all deep lacerations of the eyelids and surrounding tissues. Failure to effect the repair by approximating the various layers may cause cicatrization. Shallowing of the fornices may occur with shrinkage of the scar, and adhesions may result between the bulbar and the palpebral conjunctiva.

4. In the elderly, senile ectropion is not uncommon. Drooping of the lower lid can be corrected by a lateral tarsorrhaphy. Cautery puncture would be contraindicated on the enucleated side, because cicatrization would decrease the size of the cul-de-sac in which the prosthesis will eventually lie. There is, however, no objection to repair with cautery puncture on the side of the functioning eye.

5. Some surgeons use a conformer postoperatively. Our experience has shown this to be unnecessary, and in some instances even harmful. If a conformer is to be used, however, the selection should be of one small enough that any pressure applied will go directly backward into the socket. If pressure is inadvertently directed downward into the cul-de-sac by means of the conformer, tension may be brought to bear on the sutures closing the conjunctival wound. This may cause extrusion of the implant. Conformers are indicated in those cases in which excessive postoperative edema is anticipated or in which subconjunctival hemorrhage occurs. In such instances, a thin contact lens type of conformer should be used. The appliance chosen should be one with the concave surface having a small radius of curvature. Conformers should also be selected with one or two holes in the center to allow for drainage of secretions. When scarring is present in the pocket of the fornix, a snugly fitting conformer will aid in reforming the cul-de-sac, and thus make a better base for holding the prosthesis.

CONFORMERS WITH RADIATION THERAPY

In cases of enucleation to be followed by postoperative radiation therapy, a suitable conformer or prosthesis should be fitted first. Failure to do this will result in shrinkage and fibrosis of the tissues, making it extremely difficult to fit a cosmetically acceptable prosthesis. When a conformer is used during the period of irradiation, shrinkage does occur, but the direction is limited and the normal size and shape of the socket are maintained.

EXAMINATION AND CARE OF ARTIFICIAL SOCKET

Every ophthalmologist has his preferred routine for examining prosthetic eyes. We have found the following method to be thorough and rapid:

1. The eye is examined grossly and compared with the normal eye. A check is made for any obvious deformities, such as the eye falling too deep into the socket, giving an appearance of enophthalmos. The prosthe-

sis should be secure, should match the other eye in color and width of the palpebral fissures, and should approximate that of the normal. The lids should close firmly and easily, and the lacrimal puncta should fall against the globe. There should be no eversion of the lower lid or falling in of the superior palpebral sulcus.

2. With a pocket flashlight, the corneal reflex is checked. A bright reflex indicates a well-polished prosthesis, whereas a dull reflex indicates erosion and collections of deposits, the source of possible irritation to the palpebral conjunctiva. This is discussed further in paragraph 8.

3. The corneal reflex is checked for esotropia, exotropia, or hypertropia with the eye in the primary position.

4. Motility is checked in the cardinal positions of gaze. It is obvious that it will be a rare prosthesis that will match a normal eye for movement; however, the ophthalmologist may rapidly determine how much motility may be expected.

5. Removal of the prosthesis is a problem only when a glass prosthesis has been used, in which case it is far more prudent to let the patient remove the eye. Plastic eyes obviate the problem of breakage.

In removing the prosthesis, the object is to permit air to enter between the prosthesis and the conjunctiva, so that the negative pressure is neutralized and the appliance may be easily removed. This is best done by pulling the lower lid down and having the patient look up. A rubber suction cup may be used. If a posterior surface of a glass eye has collapsed, it may be necessary for removal to inject air behind the prosthesis.

6. The socket is examined for any signs of inflammation, scarring, secretions, or pockets of retained secretions.

7. A comparison is made of the shape of the appliance and the shape of the socket. The periphery of a proper-fitting prosthesis should follow the basic contour of the cul-de-sac of the socket.

8. The prosthesis is examined. A dull finish or knife edges or rough edges on a plastic eye or pitting on glass eyes will indicate mineral deposits on the surface. These deposits are a constant source of irritation, causing inflammation. If allowed to persist, the irritation will cause eventual fibrosis and shrinkage of the fornices. Treatment can never be successful unless the basic cause of the irritation is removed: The prosthesis must be polished.

The posterior, or concave, surface of the prosthesis must also be checked for smoothness. The absence of a shiny-smooth appearance once again indicates protein and crystalline deposits, which may be the source of irritation to the conjunctiva. If irritation is severe, it may be contributory in the extrusion of a buried implant.

9. The patient is queried as to the length of time he wears the prosthesis before removing and cleaning it. Some physicians recommend weekly or biweekly instillations of 1:5000 solution of benzalkonium (Zephiran) chloride drops, whereas others prefer the use of antibiotic drops or ointments. It has been reported that the routine use of benzalkonium chloride causes the formation of proteinaceous deposits, which may cause irritation, discomfort, and excessive secretion.

Wearing the prosthesis for too long a period may in itself cause pitting of glass eyes and irritation. It is preferable to specify that the appliance be cleansed with soap and water at precise intervals, of one to six weeks, the frequency always depending on the individual case. Liquid petrolatum or methylcellulose alleviates discomfort and is sometimes advised.

10. In bilateral enucleation, or in cases of unusual-shaped prostheses, the proper position for the insertion of the appliance may be determined by looking for a crotch between the nasal tip and the apex of the superior periphery, which is concave. The prosthesis is designed to fit over the trochlea and the tendon of the superior oblique muscle; thus, a left prosthetic eye may be

easily distinguished from a right. The scleral portion is longer temporally than the counterpart on the nasal side.

11. In cases in which treatment has been delayed, progressive stretching of the socket will be necessary before the final fitting of the prosthesis.

ANOPHTHALMOS AND MICROPHTHALMOS

Included in our series were several cases of anophthalmos [6] and microphthalmos.[11] Contrary to the belief of many ophthalmologists, best results are obtained if fittings are started at an early age. The object is to increase the size of the prosthetic appliance gradually over a period of years and thereby aid in the normal development of the lids and other soft tissues lining the orbital bone margins.

Several cases of bilateral retrolental fibroplasia were seen in which the bony parts were well developed but the lids were small, since the globe in the orbit was not of adequate size to induce stretching and provide sufficient stimulus for growth.

During infancy and childhood the tissues grow rapidly; stretching at that period occurs readily. Some believe, therefore, that if fitting is not done early, normal growth of the bones may not take place and a permanent malformation of the bone structure may occur. Our experience has not borne this out. The only cases of arrested bone development followed prolonged periods of radiation therapy. Early fitting is preferable when possible in order to have the advantage of normal stretching and development of the fornices. This will favor a good cosmetic result with maximum motility.

It is difficult to fit an anophthalmic person who has reached adulthood. The procedure is painstaking and requires stretching of the conjunctiva and cul-de-sac.

Microphthalmic, nonseeing eyes (Fig. 2*A* and *B*) are fitted in a manner similar to that described for traumatic phthisical eyes. Motility is generally good, as the muscles are intact. Our experience has not borne out the contention that the prosthesis may be a fac-

Fig. 1 (Case 1).—*A, B, C, D,* progressive stages, from injury through repair and appliance in place.

Fig. 2 (Case 2).—*A*, eye socket before conformers of graduated size were worn with pressure dressing. *B*, after conformer treatment, with lids distended. *C*, lids relaxed after conformer treatment. Note definite lower lid margin, suggesting deepened lower cul-de-sac. *D*, method of exerting pressure on conformer: suction cup with end cut off; flange end of suction cup over anterior surface of conformer; Scotch tape holding suction cup in place. *E*, patient wearing prosthesis.

tor in sympathetic ophthalmia. Some surgeons would rather enucleate such an eye, on the ground that one never knows when a nonfunctioning eye may be harboring a tumor.

REPORT OF THREE CASES

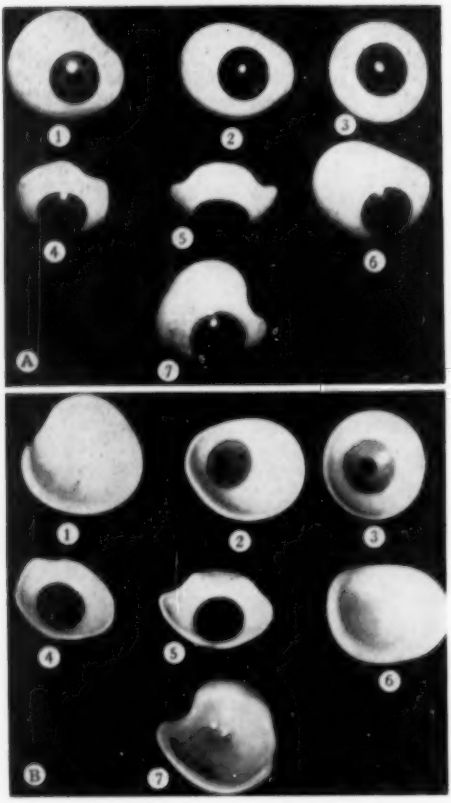
CASE 1.—M. S., a Negro man aged 42, was struck by an automobile. As he fell to the ground, his glasses were shattered, with through-and-through lacerations of the left upper and lower lids and a deep laceration on the left side of his face. There was a deep corneoscleral laceration, vitreous loss, and total hyphema. There was questionable light perception and no projection. The eye was exceedingly soft. Vision in the right eye was 20/50 without correction.

Repair was done about six hours after injury. With use of local anesthesia, the corneoscleral laceration was repaired with 6-0 black nonabsorbable surgical (silk) sutures, and the lid lacerations were repaired in layers with 6-0 black silk. The margins of the lids were sutured together to maintain proper configuration. The patient was treated with 4500 units of tetanus antitoxin; an initial dose of 600,000 units of penicillin, and a course of typhoid therapy.

By the seventh postoperative day, edema had subsided sufficiently to permit removal of all sutures except those on the lid margins. On the eighth day, the tarsorrhaphy was opened.

Twenty-two days after the accident, the left eye was enucleated and the globe was replaced with an 18 mm. Mules sphere. A small plastic conformer

Fig. 3 (Case 3).—*A*, eye socket showing ectropion of lower lid. *B*, pressure conformer in position. *C*, finished prosthesis worn by patient.



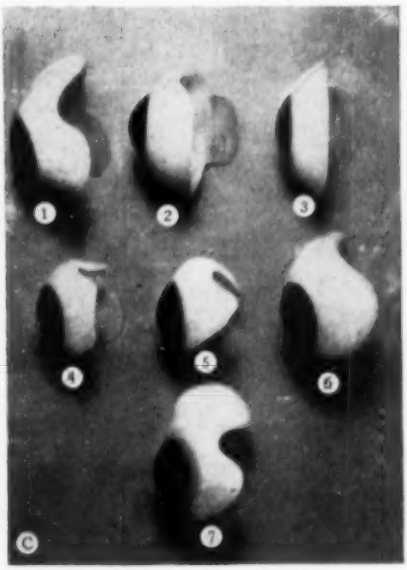


Fig. 4.—Types of prosthesis: (1) Snellen reform eye; (2) shell eye; (3) cosmetic contact shell; (4) shelf type; (5) curl-back type; (6) peanut re-form type; (7) superior build-up. *A*, anterior view; *B*, posterior view; *C*, side view.

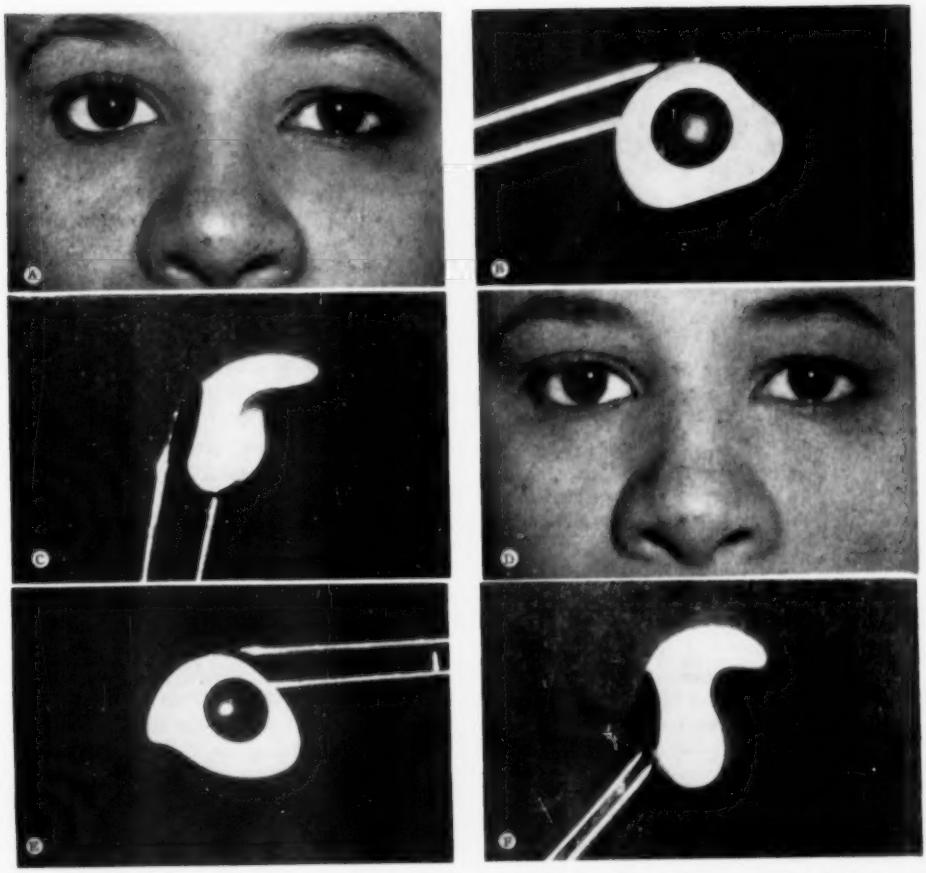


Fig. 5.—Another case, not reported in text. *A*, patient wearing an improperly fitted prosthesis, which caused drooping of the lower lid. *B*, front view of prosthesis shown worn in *A*. *C*, side view. *D*, same patient, wearing properly fitted prosthesis, permitting lower lid to resume normal position. *E*, front view of corrected prosthesis. Note concave periphery along inferior temporal side of eye, allowing lower lid to come up to normal position. *F*, side view of corrected prosthesis. Note superior peripheral curl-back used for leverage in superior fornix to permit altering of the inferior periphery.

Fig. 6.—Appearance in another case, not reported in text. *A*, before prosthetic fitting; *B*, patient wearing cosmetic contact shell.

and pressure dressing were kept in place for five days. The patient was fitted with a plastic made-to-order prosthesis. The cosmetic result was excellent (Fig. 1*A*, *B*, *C*, and *D*).

CASE 2.—R. C., a Negro boy aged 9 years, had had his left eye enucleated in January, 1950; a Guyton implant was left in place. The next month a repair was done, and two months after that the original implant was removed and replaced with a Troutman implant. A reimplantation was done in April, 1950. On Jan. 29, 1951, the Troutman implant was removed and an Ivalon sponge implant was inserted.

In March, 1952, the patient was no longer able to retain a prosthetic eye, owing to generalized contraction of the socket and a deficiency of the inferior fornix.

When first seen by us, in February, 1954, the patient had not worn a prosthetic eye for nearly two years. The socket was enlarged by using a pressure conformer, as illustrated, with weekly increases in the diameters. The pattern of the conformer was constantly maintained. On May 21, the final fitting of a curl-back type of eye was completed. The patient has experienced no difficulty in retaining this prosthesis (Fig. 2*A*, *B*, *C*, *D*, *E*).

CASE 3.—A Negro woman, aged 32, had had an eye removed at the age of 3 years. The cause was unknown. Ectropion of the lower lid was caused by a scar in the inferior cul-de-sac. The patient was unable to retain a prosthetic eye. Surgery to deepen the lower cul-de-sac was advised.

The patient was fitted with a curl-back conformer, and pressure was exerted by a suction cup attached to the anterior surface of the conformer, which was taped in position. The conformer was enlarged every two weeks for a six-week period, after which the patient was fitted successfully with a prosthesis. An excellent cosmetic result was obtained (Fig. 3*A*, *B*, *C*).

SUMMARY

1. The Galeski classification of ocular prosthesis is modified, bringing it up-to-date with newer developments.

2. Recommendations are made regarding the preparation of the socket with a view to fitting a prosthesis with the best functional and cosmetic result. The same principles apply here as in general surgery: The operation should be accomplished with a minimum of trauma and with the greatest possible tissue preservation. The strict application of this principle will insure the most motility and the least likelihood of extrusion and infection.

3. The choice of implants is discussed. Our experience has shown that, with due consideration of all the advantages and disadvantages, the Mules sphere has proved its worth above all other types of implants. It is spherical, as is the eye; therefore, it is the most anatomic of prostheses. A sphere has no points of friction; consequently, neither infection nor necrosis can be caused by pressure points.

4. The general principles in the examination and care of the artificial eye and socket are set forth. Care of the prosthetic eye should be the same as care of any other type of prosthesis. If there is a point of friction injuring the tissue, obviously the prosthesis should be removed for correction. If all goes well, the prosthesis should not be disturbed except to be kept clean, but that does not mean removal for cleansing every 10 minutes; rather, this should be only at reasonable intervals, according to the requirements of the individual case.

5. Considerations in the fitting of ocular prostheses in cases of anophthalmos and microphthalmos and following irradiation are presented.

6. Three case reports from our series of 600 cases illustrate (*a*) the necessity of preservation of tissue to insure a good cosmetic result, and (*b*) the use of a pressure conformer to create a new fornix, so that a prosthesis may be retained.

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News and Comment

GENERAL NEWS

Spring Congress, Gill Memorial Eye, Ear and Throat Hospital.—The Gill Memorial Eye, Ear and Throat Hospital, in Roanoke, Va., will hold its 29th Annual Spring Congress in ophthalmology and otolaryngology and allied specialties, April 2-7, 1956.

Among the guest speakers who will attend are the following:

Dr. Rudolf Aebli	New York
Dr. Sam Blank	Philadelphia
Dr. John E. Bordley	Baltimore
Dr. Virgil S. Casten	Boston
Dr. Jack S. Guyton	Detroit
Dr. Bayard T. Horton	Rochester, Minn.
Dr. Curwood J. Hunter	Cincinnati
Dr. John R. Lindsay	Chicago
Dr. John E. Magielski	Ann Arbor, Mich.
Dr. Stephen J. H. Miller	London
Dr. Peter N. Pastore	Richmond, Va.
Dr. Herbert J. Rinkel	Kansas City, Mo.
Dr. C. Dwight Townes	Louisville, Ky.
Dr. Everett R. Veirs	Temple, Texas
Dr. Henry P. Wagener	Rochester, Minn.

Florida Midwinter Seminar.—The 10th Annual University of Florida Midwinter Seminar in Ophthalmology and Otolaryngology will be held at the Sans Souci Hotel in Miami Beach, Jan. 16-21, 1956. The Midwinter Convention of the Florida Society of Ophthalmology and Otolaryngology will meet concurrently with the Seminar on Wednesday afternoon, Jan. 18; all registrants are invited to attend the meeting and the informal banquet which will follow.

The lectures on ophthalmology will be presented on Jan. 16, 17, and 18. Lecturers for these courses will be Dr. Francis H. Adler, Philadelphia; Dr. A. Gerard DeVoe, New York; Dr. Michael J. Hogan, San Francisco; Dr. C. Wilbur Rucker, Rochester, Minn.; and Dr. A. D. Ruedemann, Detroit.

The lectures on otolaryngology will be presented on Jan. 19, 20, and 21. Lecturers for these courses will be Dr. Frederick A. Figi, Rochester, Minn.; Dr. Lewis F. Morrison, San Francisco; Dr. John R. Lindsay, Chicago; Dr. Bernard J. McMahon, Clayton, Mo., and Dr. Charles E. Kinney, Cleveland.

Registration should be completed as soon as possible. For further information, write to Walter T. Hotchkiss, M.D., 541 Lincoln Rd., Miami Beach, Fla.

Studies on the Clinical Investigation of Retinal Correspondence

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and
HELVI SWANLJUNG, M.D., Helsinki, Finland

The number of recent publications on the clinical investigation of the status of the sensorial retinal relationship of patients with strabismus is an indication of the interest which this subject arouses among ophthalmologists. We have undertaken, on the suggestion of Dr. Hermann M. Burian, to evaluate some of the tests which have lately been reported and to elucidate their physiologic basis. In the present paper we shall report our results obtained with the prism rack test of Rønne and Rindziunski and on tests utilizing the phi phenomenon.

PRISM RACK TEST

Our study was primarily stimulated by the publication of an article by Rønne and Rindziunski,[1] in which they theorize on the pathogenesis of anomalous retinal correspondence and utilize for the first time a test which they call the prism rack test. In this test the eyes of the patient are individually exposed to a vertical bar of light. The patient observes these after-images, projected on the tangent scale or a wall, and a prism rack with horizontal prisms is moved quickly up and down before one of the eyes. Upon questioning, the patient reports that the distance between the after-images changes while the prism rack is moving. This can happen in several ways; after-images originally showing normal correspondence may be separated, moving to and from each other, or after-images originally abnormal come partly or completely together during the movement of the prism rack. Often these movements are practically continuous, but sometimes they proceed in a more jumping fashion. Sometimes they change rhythmically with the movement of the rack; sometimes it is observed that originally normal after-images become anomalous and continue to be perceived abnormally, at least for some time.

Rønne and Rindziunski state that the value of the test lies in the fact that in several squint cases it is the only test which shows that normal correspondence is beginning to break down, and, moreover, it can sometimes demonstrate that cases which with all other tests are obligatorily anomalous have some trace of normal correspondence.

The authors explain their results on the assumption of a change in correspondence, i. e., a change in perception based on a cortical process, because the localization of the after-image on the retina is constant. Exact details on the technique and the observations are lacking.

The behavior of the after-images as reported by Rønne and Rindziunski was surprising to us, because it was difficult to understand the effect of a prism bar on the relative positions of after-images, since these are interpreted centrally. We thought it worth while, therefore, to repeat the work of these authors.

Submitted for publication Aug. 22, 1955.

Supported by a grant from the American Optical Company to Dr. Hermann M. Burian.

From the Department of Ophthalmology, State University of Iowa College of Medicine.

Presented in part before the Midwest Section of the Association for Research in Ophthalmology, April 30, 1955, Rochester, Minn.

PROCEDURE

With the method suggested by Rønne and Rindziunski for the prism rack test, it was immediately apparent that two similar vertical after-images were not suitable because it was difficult to determine whether the subjects were fusing the after-images (normal retinal correspondence) or were suppressing one of them. Also, it was impossible to differentiate between the images seen by the right eye and those by the left eye. We then tried to produce dissimilar after-images by exposing the eyes to lights of different color, using colored filters in front of one eye. These after-images were not sufficiently vivid, tended to fade rapidly, and were also difficult to differentiate. Using a method suggested by Swan and Wahlgren,[2] we tried to produce dissimilar after-images using a photographic strobe light. While these were vivid, they faded too rapidly to permit adequate observation.

In an attempt to produce lasting dissimilar after-images, we developed an after-image exposure box (Figs. 1 and 2). This utilized a Type B Photoflood lamp in a fan-cooled box. A bronze mask was fastened to the face of the box, and two figures were cut into it, a vertical line with a central fixation point, and a diamond with a central fixation area. These figures were made by cutting two 1 mm. lines, separated by a strip of brass 2 mm. wide. We found that the floodlight was too bright to gaze at through a large opening. The 1 mm. lines cut out most of the glare and yet produced an after-image which was large enough to be easily visible and bright enough to have sufficient persistence.

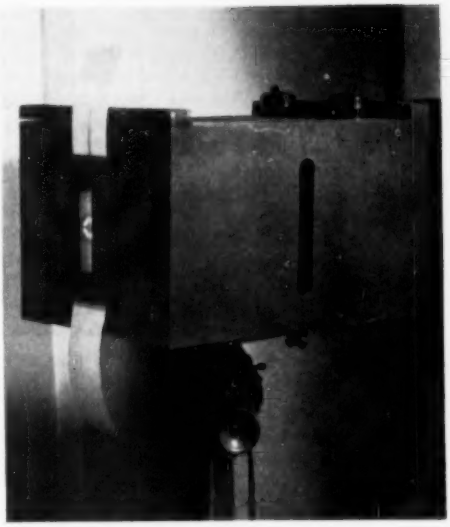

Fig. 2.—After-image box.

The eyes were alternately and individually exposed for 10 to 15 seconds to the different figures. The subjects were then asked to gaze at a lighted

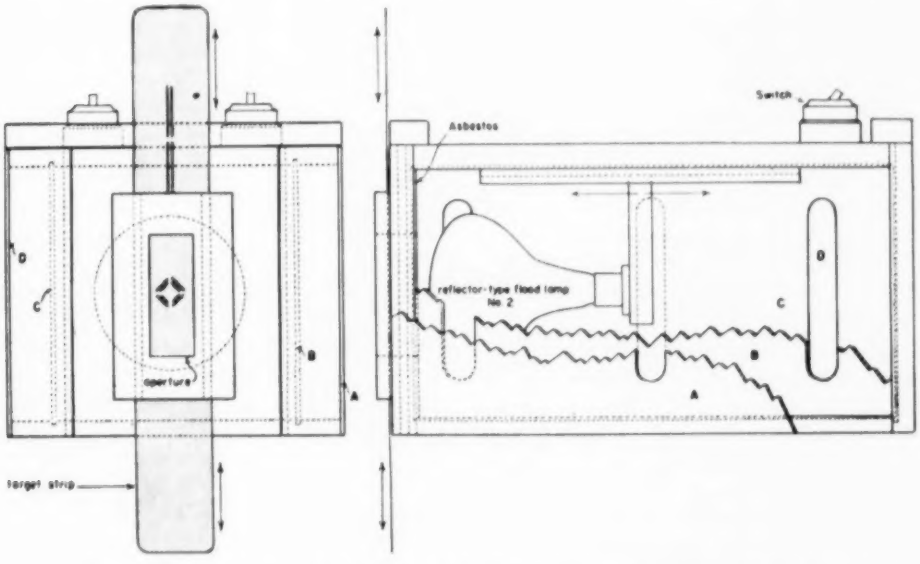

Fig. 1.—After-image box. Sides *A*, *B*, and *C* (*D*) are double walls, with ventilating holes cut in their sides. One switch controls the bulb, and one, the fan, which is located in the rear of the box. The metal target strip is held in place by spring tension but can be easily moved up and down to change the image rapidly for alternate exposure of the eyes.

surface and describe the after-image. They reported either separated or superimposed after-images. A prism bar with horizontal prisms was then placed in front of one eye and moved up and down. The subjects were asked to describe any change in the appearance or relationship of the after-images. Naturally, it was important that they did not suppress one of the images; but if they did, this was easily noted, since the eyes had been exposed to dissimilar objects.

Results

The answers we obtained with this test were in general of three kinds: (1) The after-images remained stationary in position (separated or superimposed); (2) in the case of normal retinal correspondence they moved apart, and (3) in the case of anomalous retinal correspondence they moved closer together or farther apart. In most cases, when a change in relationship of the after-images was reported, the subjects described the change as taking place in a stepwise fashion.

We have recently examined in our clinic numerous patients with strabismus in an attempt to determine the stability of their retinal correspondence with this prism rack test. We were able to find 21 cases which exhibited instability of their retinal correspondence (Table). All of these patients showed anomalous retinal correspondence with the after-image test early in the course of their strabismus. Their present ages vary from 7 to 33 years, with an average age of 14½ years. The age of onset of squint, according to the parents, varied from birth to 5 years, with an average age of 14 months. All had good and essentially equal visual acuity. All were esotropes, with the exception of one, who was an exotrope. Nineteen of these patients had undergone one to four surgical procedures for their deviation. All had been operated on relatively late in the course of their squint, with an average time lapse from onset of squint to surgery of 9.2 years. As an end-result, eight of these cases showed orthophoria or a slight heterophoria. Four of these eight had fusion with amplitude on the synoptophore, and these four also had normal retinal correspondence on the diplopia test. Only 6 of the 21 patients still had definite anomalous retinal correspondence on the after-image test, while 7 had normal retinal correspondence and 8 exhibited spontaneous variation from normal to anomalous retinal correspondence. All of the 21 showed the same result on the after-image test whether positive or negative images were used. In other words, there was no evidence of instability of their retinal correspondence which could be elicited by using positive and negative after-images.

Of all the reliable subjects with strabismus examined, we found only 8 who had had an anomalous retinal correspondence and

Stability of Retinal Correspondence as Measured by Prism Rack Test

	Unstable Retinal Correspondence	Stable Retinal Correspondence	N. R. C. Controls
No. cases	21	8	6
Ages, yr.	7-33	11-23	16-26
Average age, yr.	14.5	16.5	16
Visual acuity	6/12 or better O. U.	6/12 or better O. U.	6/6 O. U.
Surgery	19 cases (1-4 operations)	4 cases (1-3 operations)	3 cases
Interval between onset of squint and surgery, yr.	9.2	9.25	.....
Resultant angle of deviation	Ortho. or slight phoria (8 cases)	Less than 12△ deviation	Less than 16△ deviation
Functional result	Fusion with amplitudes (4 cases)	Fusion with amplitudes (3 cases)	Fusion with amplitudes (5 cases)
Original after-image test	A. R. C.	A. R. C.	N. R. C.
Present after-image test	A. R. C. (6) 8 NRC ARC N. R. C. (7)	A. R. C. (4) N. R. C. (4) (operation)	N. R. C. (6)

now exhibited a stable retinal correspondence with this test (Table, second column). The two groups compare favorably in that the average age of onset of squint was 2¼ years and the average age at the time of this evaluation was 16½ years. Four of the cases had had one to three surgical procedures for correction of the deviation. Four had had no surgery. All had good, equal visual acuity. In all cases the angle of deviation had been reduced to 12Δ or less. It was interesting to note that all those who had undergone surgery now had normal retinal correspondence on the after-image test and those who had not had surgery retained their anomalous retinal correspondence. All eight failed to describe any change in relationship of the after-images.

Our control group consisted of six subjects with esotropia who had never exhibited anomalous retinal correspondence on the after-image test. None of these described any change in the after-image.

Comment

Our results would seem to confirm the findings of Rønne and Rindziunski in that there are some strabismus patients which describe a change in retinal correspondence with the aid of a prism bar. Whether this finding is of any prognostic importance with regard to the future status of the retinal correspondence has yet to be determined. However, that these patients described this change was most interesting and thought-provoking.

In an attempt to explain the mechanism of the change in retinal correspondence produced by the prism bar, three possibilities may be considered. Did the prism bar effect the change (1) by altering the position of the eyes, (2) by altering the position of a retinal image of a fixation point (phi phenomenon), or (3) by disturbing the sensorial relationship of the two eyes?

With regard to the first possibility, we were unable to notice any change in position of the eyes behind the prism bar. In any case such a change should not affect the relative position of the after-images, since this is not altered by a change in position of the eyes after exposure.[3]

The second possibility, that the prism bar might alter the position of the retinal image of a fixation point and in this way produce a shift in retinal correspondence, deserves further consideration. If the relative visual direction of the foveas could be altered while the subject was perceiving an after-image, then the position of the after-image produced at the fovea would show

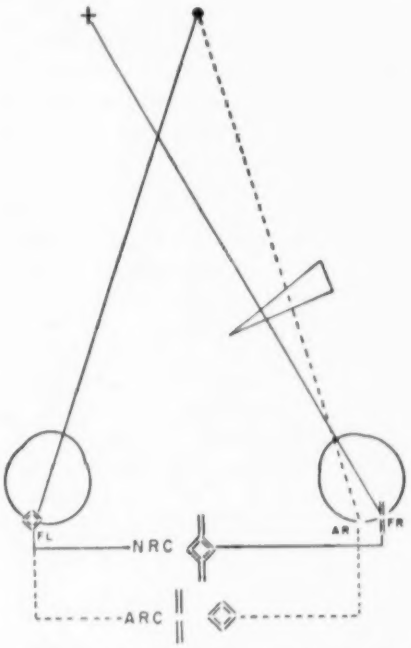

Fig. 3.—After-images in normal and anomalous correspondence.

a relative change in position. In other words, if the foveas of the two eyes could be changed from noncorresponding retinal points to corresponding retinal points, the position of the after-images relative to each other would change; i.e., they would approach each other (anomalous retinal correspondence →normal retinal correspondence). This, in effect, resembles the phi phenomenon.

In Figure 3, dissimilar after-images have been produced at the foveas of the two eyes.

If we consider, first, that the foveas do not have a common visual direction (anomalous retinal correspondence), then the fovea of the left eye (F_L) has a corresponding point (A_R) in the right eye. The after-images are interpreted as crossed after-images, since F_R is temporal to A_R and has, therefore, a nasal visual direction. The subject is now asked to fixate a point O with the left eye. This fixation point will be imaged at F_L and A_R. A prism bar, base out, is now placed in front of the right eye and moved up rapidly to increase the base-out prism effect. The prism causes a shift in the position of the retinal image of O from A_R toward F_R and in so doing may act as a stimulus to reestablish the normal relationship of the two foveas. The subject would then interpret the after-image previously produced in the right eye as shifting its location from nasal to central, and the two after-images are superimposed (normal retinal correspondence). Such a change from anomalous to normal correspondence when a light spot was moved through the visual field of the deviated eye has been observed by Burian.[4] The shift in position of the fixation point O from A_R to F_R awakens or stimulates the fovea to recognize its normal innate visual direction only in those persons in whom an anomalous retinal correspondence is not firmly established or in those who are beginning to break down their anomalous retinal correspondence with orthoptic or surgical treatment.

That most of the persons treated described a step-like movement of the after-images might indicate that there was a step-like return to normal retinal relationships. This would support the theory of Travers[5] in that there was a change in retinal correspondence with each increase in the strength of the prism. In other words, during the adaptation process in the production of anomalous retinal correspondence there were several points between F_R and A_R which developed some degree of sensorial correspondence with F_L. When the return to normal retinal correspondence occurred, each of these areas was, in turn, stimulated by the image of the fixation point O until the point F_R was reached.

For this theory to be true, one would expect that (*a*) a fixation point would be necessary in order that the prism could alter its position on the retina, and (*b*) that the direction of the prism would alter the sensorial retinal relationship accordingly. In other words, if the subject were an esotrope with anomalous retinal correspondence, a base-out prism would convert him to normal retinal correspondence. The reverse would also be true. However, of the 21 patients who demonstrated instability of their retinal correspondence with this test, only 3 were definitely influenced by the direction of the prism. These subjects were all esotropes. When they were exhibiting anomalous retinal correspondence with the after-image test, they could be changed to normal retinal correspondence with base-out prisms; and when they localized normally, they could be changed to anomalous retinal correspondence with base-in prisms. Three showed no change without a fixation point or when viewing a blank wall. The other 16 cases in this group seemed to show the instability with and without a fixation point, and the direction of the prism apparently had no effect on the response. It was difficult, however, to be sure that all these patients were fixating. We wonder, too, whether the blank wall at which they were gazing might not have texture, giving visual clues strong enough to produce a retinal image. Could it not also be possible that any change in position of a retinal image, nasal or temporal to an anomalous retinal point in a subject with an unstable anomalous retinal correspondence, would stimulate a return to the normal retinal relationships?

It is interesting to speculate on what would have happened to the after-images had we used a counterrotating prism. Would the change in position be smooth or still in a step-like fashion? If this examination were done in a completely dark room, would there be any change in position? These problems will be investigated further.

The third possibility by which this phenomenon might be explained is the alteration of the relative sensorial relationships of the two eyes. Anything which tends to subject the eyes to an environmental or a sensorial change to which the eyes are unaccustomed may change the sensorial retinal relationships. It is well known that retinal correspondence in strabismus is rarely a very stable situation. It has been shown that it may vary depending on which eye is fixating during the "after-image transfer test" [6] and whether the eyes are straight or squinting.[8] Kinetic stimulation (macular massage) at the objective angle can change retinal correspondence from abnormal to normal. A change is also noted on occasion in the after-image test, depending on whether positive or negative after-images are produced.[5] We noted many times during the production of after-images that the patients would spontaneously describe a change from normal retinal correspondence to anomalous retinal correspondence or vice versa. There were several subjects who had initially normal retinal correspondence but after several attempts at the prism rack test reverted to anomalous retinal correspondence and remained fairly fixed for a period of time. However, these changes were not described in a stepwise manner, but apparently took place in one jump.

It is not difficult for us to believe, therefore, that the placing of a prism in front of one eye of these subjects exposes the eyes to an environmental change, which of itself could be the stimulus to produce the change in retinal correspondence. This, however, does not explain the stepwise manner of change, nor does it explain the return to the original type of correspondence when the prisms are reduced.

We were unable to produce enough evidence to support fully either of the two theories which have been discussed. It is likely that both of them have some merit in the explanation of the observed phenomenon.

PHI PHENOMENON

Burian [7] defines the phi phenomenon as the apparent movement of an object point occurring when retinal elements having different visual directions are successively stimulated in monocular or binocular vision. No apparent movement is noted if the retinal elements have the same visual direction.

The use of the phi phenomenon in evaluating anomalous retinal correspondence has been mentioned occasionally in the literature. It was the belief of Verhoeff [8] that this test was so sensitive that in nearly all subjects with comitant strabismus it could be shown that the phi phenomenon was obliterated. Franklin [9] has mentioned that this phenomenon can be used to differentiate heterophorias from heterotropias. Because this test more closely approximates normal seeing conditions, it has been suggested that it is the most sensitive test in evaluating retinal correspondence.

We used the contraocular phi phenomenon to test for abnormal retinal correspondence. The subject was asked to fixate a light at either 35 cm. or 6 meters and the eyes were alternately occluded. The subject was then asked to describe any change that occurred in the position of the fixation light. It was important that the rate of alternation not be so rapid as to allow fusion of the object and not be slow enough to permit the object to be viewed separately.

Nearly all the patients examined by this method, who had either a heterophoria or a heterotropia, described some movement of the fixation object. We were unable to differentiate between heterophorias and heterotropias, and only in those strabismic subjects with harmonious anomalous retinal correspondence was the phi phenomenon absent. The reason for these results is easily understood when one considers Figure 4.

Let us first suppose that this subject is esotropic with normal retinal correspondence. When the right eye is occluded, the fixation point O is imaged at the fovea F_L. When the occlusion shifts from the right eye to the left, the fixation point O is imaged

at point A in the right eye. Since point A is nasal to the fovea, F_R, the fixation light will appear to have shifted its position from left to right. It is important to remember that the apparent shift in position of the fixation point takes place before the right eye shifts its position to take up fixation. Since the visual direction of A is temporal to that of F_R, the apparent shift in position of the fixation point is to the right. This would be true whether the subject had esophoria or esotropia.

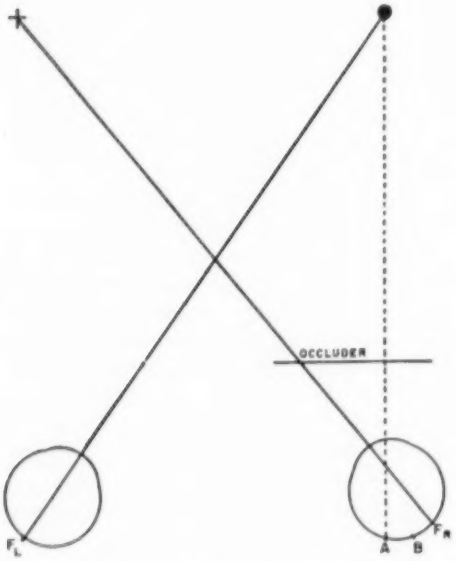

Fig. 4.—Schematic presentation of the production of the phi phenomenon.

Now let us suppose that this patient has nonharmonious anomalous retinal correspondence. If the right eye is occluded, the left fovea, F_L, fixates the light O. Shifting the cover from the right eye to the left produces an image of O at point A on the retina. Since in this subject the retinal element B in the right eye has sensory correspondence with F_L, the image of point O still falls on a nasal retinal area. The apparent shift in position of the fixation light would again be in a temporal direction. The only difference would be in the amount of the apparent shift, which would be less than in the subject with normal retinal correspondence.

From this it is easy to understand that the phi phenomenon will be absent only in persons with harmonious anomalous retinal correspondence. The fixation light O will be imaged at A, which has a common visual direction with F_L, and there will be no apparent shift in the position of the light.

Our results in the clinical application of this phenomenon would substantiate this theory. We could only determine whether a subject had harmonious anomalous retinal correspondence. The test was of no value if the subject had normal retinal correspondence or nonharmonious anomalous retinal correspondence, because in both there occurred an apparent movement. Since most strabismus cases with anomalous retinal correspondence have the nonharmonious form, we found this test of little clinical value.

Phi Phenomenon with the Major Amblyoscope

In an attempt to use the phi phenomenon to differentiate between normal retinal correspondence and anomalous retinal correspondence, one could correct the deviation with prisms and then apply this test. If any shift in the fixation point occurs, the patient has anomalous retinal correspondence; if no shift occurs, he has normal retinal correspondence. Rather than correct the deviation with prisms, Burian [9] has suggested using a major amblyoscope.

Delogu [10] recently reported using this test and was of the opinion that its accuracy and simplicity justify its employment clinically. We evaluated many subjects with strabismus, using this method. The subject was seated at the synoptophore and the arms set at the objective angle. The eyes were alternately exposed to a Grade I target, and the subject was asked to describe any shift in position of the targets. If a shift occurred, the subject was shown to have anomalous retinal correspondence.

It was our opinion that the difficulties encountered in performing this test preclude its use clinically. As with all the tests described in this paper, it requires an intelligent subject. Direction of the shift is very confusing to many patients. Because retinal correspondence was unstable in many of these subjects, there was a tendency to change from normal retinal correspondence to anomalous retinal correspondence from one movement to the next. This change in correspondence also occurred when occlusion was shifted from one eye to the other.

SUMMARY AND CONCLUSION

An attempt was made to evaluate two tests used for the investigation of retinal correspondence. The basic physiology and theories pertaining to these tests are discussed.

We conclude that the prism rack test is one of many ways by which to demonstrate instability of retinal correspondence. We suggest that the reason for the change in retinal correspondence shown by this test may be due to a change in position of a retinal image by the prism (phi phenomenon) or that the presence of the prism subjects the eyes to a sensorial or an environmental circumstance to which the eyes are not accustomed, and so stimulates a change in retinal correspondence.

The use of the phi phenomenon to differentiate between normal retinal correspondence and anomalous retinal correspondence is of little value, since this phenomenon is absent only in harmonious anomalous retinal correspondence. Neither does it differentiate between a heterophoria and a heterotropia, as has been claimed. This test can differentiate between anomalous retinal correspondence and normal retinal correspondence only when the deviation is corrected with prisms or on a major amblyoscope.

Both tests are of value in helping to understand the visual pathophysiology, but we would not recommend their clinical use, for the following reasons:

1. They require an intelligent subject, and because of this are of little value in patients under the ages of 7 to 8 years.

2. They are of no value in patients who tend to suppress.

3. The prism rack test requires the production of lasting dissimilar after-images, which, in turn, requires special instrumentation.

4. They are very time-consuming and exhaust both the patient and the examiner.

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Spasm of the Near Reflex

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The entity which we have called spasm of the near reflex [1] has been infrequently described in the literature, and then under such names as spasm of accommodation, ocular spasm, and convergent spasm. It is characterized by intermittent and usually painful convergence, accommodation, and miosis. Although reported in association with neurologic * and vestibular † disease, it is generally attributed to hysteria. Nevertheless, the cases reported have been isolated instances, and, except for a collation of cases in Wilbrand and Saenger's text,[7] no comprehensive series has been reported heretofore.

We have had the opportunity to study 16 cases. It is our purpose to summarize these cases with specific reference to signs and symptoms, age and sex, etiologic factors, and treatment. These cases are presented individually in the "Addendum." It was found impossible to review adequately the cases in the literature, for, while some clear-cut instances have been described, the majority are not sufficiently documented to be accepted unreservedly; most are included with other cases of accommodative or convergent spasm that is different from the entity with which we are concerned. Yet typical instances have been reported by Fuchs,‡ Paton,[9] Prangen,[10] Zentmayer and Reese,[11] Bielschowsky,[12] Souders,[13] Holt,[14] and Walsh.[15]

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* References 2 to 4.

† References 5 to 7.

‡ Fuchs,[8] cited by Wilbrand and Saenger.[7]

SIGNS AND SYMPTOMS

Spasm of the near reflex was manifested in the present patients by the intermittent occurrence of convergence, accommodative spasm, and miosis. The convergence was variable in degree but amounted to as much as 50 degrees in some of the patients. The accommodative spasm was difficult to measure because of its continual fluctuation, but in several of the younger patients it was estimated by retinoscopy to be 8-10 D. The miosis was also variable, although always present and usually extreme. The attacks usually lasted only a matter of seconds or minutes and tended to be distinctly uncomfortable to the patient. In consequence the patients squinted up their lids and gave the appearance of being photophobic or of having blepharospasm. Maintained convergence did occur on occasion and led to the mistaken impression of a sixth nerve palsy.

The attacks were frequently precipitated by attention directed to the eyes. Thus, in over half of the patients of the present series, an attack could be repeatedly produced by manipulation of the lids or by shining a light into the eyes. Other common precipitating factors were asking the patient to read the visual acuity chart or to look in one or the other direction.

The symptoms of which the patient complained were usually those of blurred vision (13 cases) and diplopia (10 cases). Also common were headache (nine cases), dizziness (seven cases), pain in eyes (six cases), and difficulty in walking (six cases). In general, patients with spasm of the near reflex had a plethora of symptoms, not necessarily related to the eyes.

Atypical were cases in which spasm of the near reflex occurred with attempted gaze in one specific direction. Thus, one patient (Case 15) developed a spasm only when she was *asked* to look to the right, but no spasm developed when she looked to the right in random fashion. Another patient developed the spasm on voluntary upward gaze only.

The period over which the attacks occurred could not be accurately determined, for return examinations seemed to reevoke the symptoms. In no case, however, was the period for untreated spasms less than several weeks, and in one case at least it was unchanged with examinations over a four-year period. Others gave histories suggestive of having had the condition much longer.

AGE AND SEX

The onset was commonest between 15 and 20 years of age, but no period was exclusively associated with it. Thus, three cases began between 10 and 15 years; five cases, between 15 and 20 years; two cases, between 20 and 25 years; two cases, between 25 and 30 years; two cases, between 30 and 35 years, and 2 cases, between 35 and 50 years.

Most striking was the predilection for females. Thus, only 3 of the 16 patients were males.

ETIOLOGIC FACTORS

Of the 16 patients, only 2 had definite neurologic disease. One (Case 8) had a cerebellar tumor, and one (Case 11) had had cerebral palsy since birth. Two patients (Cases 4 and 10) also had symptoms suggesting labyrinthine hyperexcitability. On the other hand, 11 were thought to be emotionally unstable, and 8 had had a diagnosis of hysteria. Other manifestations of hysteria, such as tubular fields, were occasionally present. Nevertheless, several patients had been studied and were being studied extensively as organic disease suspects when the syndrome was recognized, and one (Case 16) had had numerous surgical explorations, including a craniotomy for a suspected lesion. Trauma was noted in the history by three patients (Cases 1, 2, and 5).

A phoria or some anomaly of binocular fixation might be thought to be a predisposing factor, but no such constant defect was to be found. Thus, an esophoria was present in four cases, an exophoria in one case, an exotropia with unilateral blindness in two cases, and a variable esophoria and exophoria in three cases.

TREATMENT

Various therapeutic procedures were tried but without systematization. Two of the patients (Cases 2 and 11) had observed that they could relieve their spasm by tilting the head to one shoulder, and two patients (Cases 12 and 14) had found they could get relief by turning the head to one side. Atropinization was tried in seven cases, with complete relief in four and partial relief in three. Minus lenses which would partially compensate for their accommodative spasm were tried in 10 cases, with definite improvement in vision and loss of subjective complaints in all instances.§ Four cases were not treated and improved spontaneously so far as our follow-up studies could determine. One patient (Case 13) had extensive orthoptic exercises but continued to have the spasm of the near reflex. It may well be that, as Souders [13] suggested, treatment which continues to direct the patient's attention to the eyes may perpetuate the abnormality.

COMMENT AND CONCLUSIONS

Spasm of the near reflex is a distinct entity, not to be confused with convergence excess or isolated "spasm of accommodation." It may rarely be associated with neurologic disease but is most commonly a functional disturbance that is properly called hysteria. The spasms are usually precipitated by attention directed to the eyes.

The entity occurred at various ages but was most frequent in our series in the late adolescent period. It is much commoner in females than in males.

§ It is somewhat paradoxical that minus lenses should relieve a convergent strabismus. Plus glasses often made the spasm worse.

Specific treatment consisted in either atropinization or the use of minus lenses for as long as necessary. Probably contraindicated are such procedures as orthoptic exercises, which continue to focus the patient's attention on the eyes.

ADDENDUM

CASE 1.—A 22-year-old single woman, complained of "headache and visual disturbance" since an automobile accident one month previously. She had consulted several physicians on account of blurring of vision, diplopia, nervousness, insomnia, and pain in the right arm and shoulder. The patient stated she had been aware of something wrong with her vision immediately after the accident, when she had looked at a neon sign and saw that it was blurred. A lawsuit was pending.

Physical examination and pertinent laboratory studies (EEG, skull x-rays, lumbar puncture) were all negative. The psychiatric consultant felt that this was not a compensation neurosis but that the patient was overreacting to the accident in a manner compatible with hysteria.

Examination of the eyes was difficult in that any attention to the eyes precipitated a spasm of convergence (approximately 50 degrees), an accomodation (estimated by retinoscopy to be 8 D.), and a miosis (from a pupillary size of approximately 5 mm. to one of 2 mm.). Vision could not be improved to more than 20/200 even with minus lenses. Visual fields showed a general constriction compatible with the tubular type but were of questionable reliability. The patient did not return for cycloplegic refraction or for therapy, and follow-up correspondence has remained unanswered.

Noteworthy features of this case were the possible relation to an accident and the association with generalized constriction of the fields, such as is often associated with hysteria.

CASE 2.—A 20-year-old woman was brought to the emergency ward by her foster mother because of episodes of fainting, amnesia, difficulty in walking, ocular spasm, abdominal pains, nausea, and vomiting. These symptoms began three weeks previously, when the patient fainted and fell, striking her head. She was hospitalized elsewhere for this and had been depressed since discharge from the hospital. The patient was described by her foster mother as being "flighty and emotionally unstable." She had been allegedly seduced three years previously, and the offspring was now in a foster home. The patient had attempted suicide two years previously. Five months prior to the present hospital admission the patient was married but was deserted by her husband after nine days. She is said to have had various symptoms similar to those at present brought on by unhappy events in her life.

General examination showed the patient to be depressed and uncooperative. No neurologic abnormality was found. The eyes at first revealed no gross abnormality, but any attempt to examine them resulted in a prompt and painful convergence (about 30 degrees), miosis, and accommodation (estimated by retinoscopy to be 8-10 D.). With minus lenses the vision could be improved only to 20/200, but cooperation was too poor for either accurate acuity measurements or field study. It was noted, however, that the patient tilted her head to her right shoulder and seemed to be less bothered by the diplopia in this position.

The patient was admitted for study but was such a problem on the ward (setting fire to a sofa, breaking dishes, etc.) that she was discharged and has not returned.

This patient, who was obviously an unstable person with a multitude of symptoms, had had several previous episodes that may have been spasms of the near reflex associated with emotional upsets. The onset of the present episode may have been related to trauma. While the effect was not clear-cut, the patient seemed to obtain some relief from the spasms by tilting her head.

CASE 3.—A 14-year-old boy was said to have developed dizziness, diplopia, and blurring of vision while in school a few hours prior to the present examination. He was also said to have had some difficulty a few years previously for which several lumbar punctures were done, but no further details of this episode could be obtained.

Neurologic examination suggested diminution of all modalities of sensation over the left side of the body but no other significant abnormality. Skull x-rays, spinal fluid, and all other laboratory tests were negative. Examination of the eyes showed initially a convergent strabismus of approximately 25 degrees in the primary position but orthotropia on looking to either side. There was no limitation of gaze, but a fine pendular nystagmus, most marked in the abducting eye, was present on gaze to either side. The visual acuity was 20/200.

While undergoing refraction, the patient observed that his vision momentarily cleared, and it was observed that the myopia, which was estimated by retinoscopy to be 4-5 D., simultaneously disappeared, as did the miosis and convergence. Moreover, it was found that placing a —1.00 sphere before his eyes resulted in orthotropia, emmetropia, and an improvement of vision to 20/20. Similarly, 8△ prisms, base out, resulted in binocular fixation

and correction of his vision. No such effect was noted with plus glasses. With atropine cycloplegia the eyes were straight and the patient's vision was normal. The patient then had an esophoria of 12△ for distance and 25△ for near.

The patient was given —1.00 spheres to use and was symptomatically cured.

This case was unusual in that the spasms were occasionally continuous over some period of time and were not apparently painful or disconcerting to the patient. The case was also unusual in that there was no evidence of emotional instability or other hysterical manifestations. Finally, the dramatic "cure" by minus lenses is of interest and practical significance. Photographs of this patient showing the effect of glasses have previously been published.[1]

Case 4.—A 45-year-old housewife was admitted to the hospital because of dizzy spells and headaches of three to four months' duration. One year previously she had had a subjectively similar episode that had lasted three weeks. The dizzy spells were described as a true vertigo with illusory rotation of the environment clockwise. These attacks were precipitated by sudden active movements of the head and lasted only a few seconds. They also occurred when the patient looked upward or when she rolled over in bed. The patient's headaches were situated in the occipital region and were of the "pressure" type. The patient had no tinnitus, nausea, or vomiting and volunteered no visual complaint.

Neurologic investigation, including EEG, skull x-rays, isotopic cerebral localization, spinal fluid studies, and caloric tests, revealed no abnormality.

The patient's eyes were normal most of the time, and the visual acuity was then 20/20. The eyes were orthotropic with a slight exophoria (1.5△), and the movements were full. But sudden movements of the patient's head resulted in a prompt convergence, miosis, and blurring of vision from accommodative spasm.

In this patient manipulation of the lids or shining a light into the eyes did not evoke an attack.

Noteworthy in this case, and rarely in others, was the apparent relation of the spasms to labyrinthine stimulation. This undoubtedly bears on Borries' observations [4] of the association of spasm of convergence (?) with labyrinthitis.

Case 5.—A 19-year-old truck driver came to the eye clinic with the complaint of "not being able to see." This began two days previously, shortly after falling over a chair and striking his head at the home of his girl friend. Approximately 15 minutes after this incident everything "seemed to black out" and he "couldn't see any more." However, his vision suddenly and completely returned two hours later and was normal until a few hours prior to the present visit, when he again struck his head on a storage bin while at work, and again everything "blacked out." This latter episode was interrupted by brief periods of clear vision.

Examination at first showed that the eyes were in the primary position and the visual acuity was occasionally 20/20, but any manipulation of the lids resulted in marked convergence, miosis (1 mm.), and a myopia of approximately 8 D. The acuity then fell to 10/200 or less. Under atropine cycloplegia his vision was 20/20 in each eye without correction; he was then orthophoric, and no spasm of convergence could be evoked.

Aside from suggestive relation to trauma, this case is of interest in showing the apparent "cure" while the patient was under atropine cycloplegia.

Case 6.—A 36-year-old unmarried clerk had been followed by various clinics in the outpatient department for a variety of complaints, including nervousness, palpitation, dizzy spells, headaches, nausea, vomiting, diarrhea, heat intolerance, tinnitus, excessive sweating, and "fear of death." In the past 10 years she had been admitted to the hospital 19 times and had had four abdominal operations, including uterine suspension, cholecystectomy, and hysterectomy. She was admitted to the neurologic wards because of bizarre neurologic symptoms and convergent strabismus, but no abnormality was found except in the eyes, and a diagnosis was made of hysteria, anxiety, and depression.

Examination of the eyes showed intermittent convergence, accommodation, and miosis elicited by manipulation about the eyes (as by elevating the upper lid or depressing the lower lid) or by shining a light into the eyes. During the convergence, the pupils changed from approximately 6 to 3 mm., and the visual acuity decreased to less than 20/200. In relative darkness and at rest, the patient's eyes were orthotropic, with only a slight esophoria. The visual fields were normal.

The patient's eyes were not further examined or treated, but during the subsequent year she became progressively depressed, with suicidal tendencies, and was eventually institutionalized. Follow-up correspondence revealed that the diagnosis was psychoneurosis, and the patient was discharged after a series of shock treatments.

This case illustrates the multitude of symptoms which patients with spasm of the near reflex are prone to have and the obvious

psychoneurotic background upon which the spasms are superimposed.

CASE 7.—A 36-year-old draftsman had complained of transient blurring of vision since the age of 18, the attacks increasing in frequency of late. He had been moderately deaf since infancy and had recently started wearing a hearing aid.

Examination of the eyes showed a spasm of convergence, miosis, and accommodation whenever the patient attempted to look up or whenever his lids were manipulated or pressure was made against his forehead. These spasms were relieved by placing minus spheres (1-4 D.) before his eyes. The ocular movements were full, but it was noteworthy that fine pendular oscillations of the eyes occurred with the spasms of convergence. These did not exceed 3-4 degrees and were extremely rapid (20-50/sec.), similar to what one sees occasionally with voluntary nystagmus. Yet the patient could not induce them voluntarily. The patient refused psychiatric consultation, but one year later, when the patient was hospitalized for repair of an anal fissure, no ocular abnormalities were noted.

Unique in this patient were the fine oscillations of the eyes associated with the convergence. While unexplained, they did not resemble the nystagmus seen with neurologic disease. They did, however, resemble the oscillations of the so-called voluntary nystagmus, which has also been reported as occurring with hysteria.[16]

CASE 8.—A 22-year-old housewife was admitted to the hospital with a posterior fossa tumor. Her presenting symptoms were failing vision and unsteadiness of gait. The eyes showed papilledema, secondary optic atrophy, and a reduction of vision to hand movements in the temporal fields of both eyes. On attempting to look upward or downward, there developed a spasm of convergence and miosis (accommodation was not tested). There was also a gross nystagmus on conjugate gaze to either side.

A craniotomy was performed, with partial removal of a neurofibroma of the posterior fossa, extending from the midline to the right cerebellar hemisphere.

This case represents one of the rare instances in which spasms of the near reflex were associated with an organic lesion. It is also rare in that the patient was almost totally blind.

CASE 9.—An 18-year-old woman had as chief complaints loss of vision, headaches, and double vision. These complaints began three years ago with spells of confusion, severe headache, diplopia, and "voices in the head." The patient was an illegitimate child. She was aware of this, and compounding the emotional conflict were the facts that her own mother married the brother of her adopted father, while her adopted mother showed a dominant hostility to the patient.

The neuropsychiatric consultant found no evidence of an organic lesion and suggested hysteria.

Examination of the eyes showed intermittent spasms of convergence, accommodation, and miosis evoked by manipulation of the lids or by shining a light into the patient's eyes. With this spasm was a facial expression indicating moderate pain. The accommodation amounted to approximately 8 D. during the spasm; but even when the eyes were straight, it measured approximately 5 D. Visual fields showed generalized constriction of both eyes.

Cycloplegic refraction showed O.D. +0.25 sph. $\bigcirc$ —1.00 cyl., ax. 10; O.S. +0.25 sph. $\bigcirc$ —1.00 cyl. ax. 170. Vision, however, could not be improved beyond 20/50 O.U. Despite cycloplegia, the patient continued to have intermittent convergence.

The patient was given —2.75 spheres and showed prompt and marked lessening of the spasm. At the end of six months the glasses were used only for near, and the spasms were induced only rarely with bright light or manipulation of the lids. With the Maddox rod the eyes were practically orthophoric.

This patient showed little relief of the convergence spasms by atropinization but was considerably relieved by minus glasses. The patient's background was such as one might expect to be conducive to psychologic conflicts.

CASE 10.—A 20-year-old college student was admitted to the hospital because of frontal headache, double vision, and vertigo, of one month's duration. The patient had frequently been studied in the past for symptoms suggestive of rheumatic fever and chorea, but with recurrent inferences of hysterical overlay. Since childhood she had had a series of emotional conflicts. The present symptoms began one month previously, following by one week a tooth extraction. The dizziness was said to be accompanied by an illusory movement of the environment and precipitated by her standing up or moving her head suddenly.

Physical examination showed some limitation in movement of the right shoulder and left knee, with an aortic diastolic murmur. Neurologic examination, including an electroencephalogram and spinal fluid study, were all normal.

Examination of the eyes revealed a convergence and a peculiar spasm of accommodation of approximately 5 D. (as determined by retinoscopy) when both eyes were open and gazing at a distance but not when the right eye was closed. Closing the left

eye had no effect on the spasm. With minus lenses the patient became approximately orthophoric.

Under cycloplegia the patient was approximately emmetropic, but vision was correctable to only 20/40 in O.D. and 20/30 in O.S.

The patient was also found to have a monocular diplopia of the right eye during the accommodative spasm, and there was a generalized constriction of the visual field of this eye only.

Despite the improvement with minus glasses, the patient was not treated. Eight years later she was readmitted to the hospital for treatment of an arthritis. No mention was made at that time of ocular abnormalities.

Not only did this patient represent the emotional instability characteristic of most persons with spasms of the near reflex, but the spasms themselves seemed to be related to labyrinthine hyperexcitability. The spasms were also curiously associated with "openness" of the right eye. This right eye also showed a monocular diplopia and constriction of the visual field. We have no explanation for this fixation on the right eye but assume it has some psychologic significance. As in most other patients, the spasms were lessened either by minus glasses or by cycloplegia.

CASE 11.—A 33-year-old housewife was admitted to the hospital for unexplained pain and paresthesia in the left arm, with blurring of vision and twitching of the eyelids, all of approximately two years' duration. The ocular complaints occurred in episodes lasting anywhere from a week to several months, and during these periods the patient stated she could not see gross objects a few feet away. Intense sunlight seemed to bring on these episodes. On the other hand, she had found that tilting her head to the right shoulder had occasionally relieved her symptoms, and, on one occasion, she had been temporarily helped when a cycloplegic had been given to her as part of an eye examination.

Ophthalmologic examination showed a continual twitching of the lids, most marked of the right eye, and a gross esotropia whenever an attempt was made to examine the eyes, especially when a light was shone into them. The esotropia amounted to approximately 10 degrees, and with it there was a miosis to about 2 mm. and an accommodative spasm of approximately 8 D. Visual acuity during the spasm was reduced to 5/100, but with a —8.00 sphere it improved to at least 20/40. The spasm was consistently improved by tilting her head to the right shoulder and occasionally improved by tilting to the left shoulder.

Since there was thought to be significant lessening of the spasm with minus glasses, a pair of —1.25 spheres was given to the patient to use as symptoms indicated. She reported one year later that the glasses had been of equivocal benefit.

In most respects this case was typical of the spasms of the near reflex that were evoked by any attention directed to the eyes. On the other hand, the case was unusual in being associated with twitching of the eyelids, and especially in being relieved by tilting the head to the right shoulder.

CASE 12.—A 12-year-old girl had had cerebral palsy since birth, with resultant spasticity of the lower extremities. She was of normal intelligence and a good student in school. She was referred for an eye examination because her mother and teacher had noted intermittent convergence when she applied herself attentively. This was associated with a tired feeling in her eyes, supraorbital pain, lacrimation, and headache. The condition had been present for several months, and her teacher had thought it was purposeful.

Examination of the eyes showed little or no esophoria most of the time but intermittent convergence, miosis, and spasm of accommodation whenever a light was shone in her eyes or the lids were manipulated, or even when a threatened gesture of manipulation was made. Similar spasms occurred when the patient was asked to look intently at some object, as in reading the Snellen chart. When she was asked to look eccentrically, the eyes developed a spasm of convergence, but no such spasm developed when the patient looked eccentrically in random fashion. The accommodative spasm amounted to 8-10 D.

Under cycloplegia the eyes were straight, and no spasm developed when a bright light was shone in the eyes, but convergence was brought out by manipulation of the lids. The patient's refraction was +1.00 sphere O.U., and visual acuity was 20/30.

The patient was given —2.00 spheres, and follow-up observations two months later indicated that the patient had been completely and promptly "cured" by the glasses. For the first two to three days the spasm recurred when the glasses were removed, but since then no spasms have developed on removal of the glasses, even with strong light and manipulation of the lids. Vision was then 20/20 O.U., and the eyes were orthophoric. The glasses were discontinued.

This case illustrates the paradox of spasms occurring with voluntary movements but not with random movements. The patient de-

veloped a spasm on command to look in some direction but not on haphazard gaze in the same direction. Thus, it is not associated with the movements per se but is concerned with some higher function in the general field of the psyche.

This case also illustrates the dramatic "cure" sometimes possible with minus glasses and cycloplegia.

CASE 13.—A 29-year-old clerical worker had as chief complaints increasing difficulty with vision for six months and diplopia, pain in the eyes, and exacerbation of blurred vision for three weeks. This recent exacerbation coincided with working longer hours.

Examination of the eyes revealed an exotropia of approximately 10 degrees as long as the patient was relaxed and wearing her glasses (O.D.—1.50 sph.; O.S.—0.75 cyl. ax. 90), but she developed a marked convergence, miosis, and spasm of accommodation whenever she focused at near or when she took off her glasses. Visual acuity with glasses was 20/20 O.U. It was noted, moreover, that no spasm developed so long as the patient was talking but often did occur when the examiner talked to the patient.

Under cycloplegia the patient's refraction was found to be O.D.—0.75 sph.; O.S.+0.50 sph. $\bigcirc$—0.50 cyl., ax. 90.

The patient had numerous complaints, but no abnormality other than that of the eyes was found on examination.

The patient was treated with sedative amounts of phenobarbital. No follow-up was available.

This case illustrates the fact that spasms of the near reflex may occur in persons with an exotropia. Thus, an esophoria is not, as might be anticipated, a prerequisite.

CASE 14.—An 18-year-old college student had a four-year history of intermittent blurring of vision. This involved distance vision preferentially (as in viewing the blackboard) but occasionally involved near vision as well. The attacks of blurred vision were possibly associated with fatigue but were not known to be associated with emotional upsets.

Examination of the eyes showed intermittent quivering of the lids and an accommodation of 2½ D. (by retinoscopy) and slight miosis. These attacks were precipitated by shining a light into the patient's eyes or by manipulating the lids. Between the attacks the patient was approximately orthophoric, but during an attack the eyes showed a 10△ esophoria. Under cycloplegia the patient was emmetropic, with a visual acuity of 20/20—O.U.

The patient was given —1.00 spheres and had considerable relief immediately. She used these glasses intermittently for one year as symptoms indicated but permanently discontinued them then. Follow-up observation eight years later showed she had gone through law school and had had three years of law practice, without further ocular or other symptoms.

Aside from the mildness of the spasms and the relief by minus glasses, this case is not particularly noteworthy.

CASE 15.—A 57-year-old housewife had as the chief ocular complaint blurring of vision on looking to the right. However, she had had a series of ocular and systemic abnormalities for many years. She had had high myopia since childhood, and 15 years previously had lost all useful vision of the right eye through separation of the retina. Of the systemic abnormalities, she had had arthritis, nephritis, bronchial asthma, gastric ulcer, diaphragmatic hernia, and obesity. She was also suspected at one time of having a pituitary basophilic adenoma, but this diagnosis was never confirmed.

When she was examined four years prior to the present study, the right eye showed approximately 20 degrees of exotropia, and when no attention was paid to the patient's eyes, they moved fully and conjugately in all directions. When, however, the patient was asked to look to the right or to follow a moving object to the right, the eyes showed an extreme convergence, miosis, and pain.

There was also some blurring of vision, but whether or not this was due to an accommodative spasm could not be conclusively demonstrated because of the high myopia and transient nature of the spasms. Looking to the left did not induce any such spasms.

Examination at the present time showed exactly the same abnormalities, with marked spasm of convergence and miosis and pain on voluntary dextroversion but not on random dextroversion.

This patient, with a plethora of general symptoms and a considerable number of abnormalities of the eyes (high myopia, blindness in the right eye, and exotropia) developed a painful spasm of the near reflex, which, curiously, occurred only when she was asked to look to the right. On the other hand, random movements to the right were executed fully without spasms. This observation, again, indicates the paradoxical dissociation of random and voluntary acts in producing the syndrome.

CASE 16.—A 29-year-old housewife had as the present chief complaints diplopia, blurred vision, dizzy spells, and right retrobulbar pain. During the previous several years she had had a variety of complaints and several operations. Since the birth of her third child, seven years before, she had had "weak spells," necessitating three months in a rest home. Five years previously she had had an oophorectomy, bilateral salpingectomy, and appendectomy "for cysts and inflammation." Two years previously she had had a right mastoidectomy, followed by spells of nausea, tinnitus, headaches, pain behind the right eye, and blurring of vision.

Because of the foregoing symptoms, the patient had had a ventriculogram, two arteriograms, and a craniotomy. The last revealed no abnormality within the skull. The patient's symptoms have continued without significant change.

Examination of the eyes showed a typical spasm of convergence (to about 25 degrees), miosis, and spasm of accommodation precipitated by any manipulation of the lids or by shining a light into the patient's eyes. Between attacks the eyes were orthotropic, and the patient's vision was normal. During an attack the patient's vision was improved with —5.00 spheres, but the diplopia was corrected only when 16△ were added base out.

For treatment the patient was given —3.50 spheres to wear as symptoms required.

This patient had typical spasm of the near reflex. It is reasonable to believe that she had had these attacks for some time and that the symptoms had played a major role in the exhaustive investigation to which she had been subjected. This case points up the importance of recognizing the entity and being familiar with its functional significance.

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Registry of Interesting Cases

It is the purpose of this section to record cases on the basis of interest only. No complete review of the literature is attempted and no claim for priority is implied except when specifically stated. Publication of case reports is subject to the concurrence of the Editorial Board on the interesting aspects of the case. It is requested that the reports submitted be as brief as is consistent with inclusion of the pertinent facts, bear a title that is as specific as possible, be prefaced by a paragraph that states why the author feels the case is of interest and be accompanied with photographs whenever possible.

DOUBLE LACRIMAL PUNCTA AND DACRYOPS

THE LITERATURE on supernumerary puncta and canaliculi has been surveyed by Duke-Elder [1] up to the year 1950. These anomalies are infrequently reported, although they are said to be not exceptionally rare. They are found more frequently in the lower lid, and up to four puncta have been observed. Accessory

Fig. 1.—Right lower lid partly everted to show two lacrimal puncta.

puncta may open into the normal canaliculus or into an additional one. Other anomalies of the lacrimal passages, such as fistula of the sac, may be associated, and hereditary transmission has been recorded. Abnormal outbudding of the portion of the epithelial rod from which the canaliculus and punctum develop is regarded as the cause of these anomalies. Tiberi,[3] in 1952, reported another case of double lacrimal puncta. Duke-Elder [1] and Mann [2] mention the rarity of congenital cysts of the lacrimal gland.

In the following case two fully formed lacrimal puncta, opening into a normal canaliculus, were observed side by side in the lower lid; in the same eye there was found a cyst of the lacrimal gland, also quite probably of congenital origin.

Submitted for publication Aug. 30, 1955.

From the Brooklyn Eye and Ear Hospital.

REPORT OF CASE

Y. L., a woman 61 years of age, came to the clinic of the Brooklyn Eye and Ear Hospital, service of Dr. Frank E. Mallon, on March 17, 1955, complaining of slight tearing of both eyes, but no epiphora. Her past and present general medical history was not contributory. Gross external examination showed normal eyes and ocular adnexa. There was no fullness of the lids. Investigation of the lacrimal apparatus in the right eye disclosed in the lower lid two distinct lacrimal puncta occupying a normal anatomic position (Fig. 1), both opening into a single, normal canaliculus. Moreover, a pea-sized cyst of the lacrimal gland appeared on eversion of the upper lid in the same eye (Fig. 2). The lacrimal passages of both eyes were patent. The vision of each eye was 20/25, improved to 20/15 with a +0.75 cyl ax 90 correction; with +2.50 spherical addition, near vision Jaeger #1 at 14 in. Ocular media were clear and fundi normal in all respects.

Fig. 2.—Right upper lid partly everted and globe in down and nasal gaze, exposing cyst of lacrimal gland.

SUMMARY

A woman aged 61 presented two unusual abnormalities of the lacrimal apparatus of one eye: double lacrimal puncta in the lower lid and dacryops, presumably congenital.

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TRANSIENT MYOPIA IN CASE OF DERMATITIS TREATED WITH CORTICOTROPIN

A physician aged 47 had had a myopia of essentially the same amount for the past six years: A correction of —2.75 sph ⌒ —0.50 cyl, ax 115 O. D. and —2.75 sph ⌒ —0.50 cyl, ax 90 O. S. gave him a visual acuity of 20/20. He has been wearing a reading addition of +0.75 sph for the past three years.

Ten days before he was seen for his present complaint he had contracted a severe poison ivy dermatitis of the face and hands, for which he had received four daily injections of 20 mg. of corticotropin gel and for four more days 5 mg. of hydrocortisone four times daily by mouth. The dermatitis cleared up entirely within a week. In the past two days the patient had noticed that his vision had deteriorated markedly. The distance was very blurry, while he could read with his distance glasses.

The examination was entirely negative except for a visual acuity of 20/50 O. U. with the present correction and an increase in spherical refraction from —2.75 to —3.75. With this new correction vision was 20/20 in each eye. One week later the spherical refraction had returned to —2.75, i. e., the original amount, and with the additional cylinder vision was 20/20 again.

An attempt to explain this temporary change of refraction can only be pure speculation. An increase of refraction (usually of 2 to 3 D.) is not uncommonly observed in sudden onset or sudden deterioration of diabetes. The patient's blood sugar concentration, while the refraction was still at its abnormal height, was 77 mg. per 100 cc. one and one-half hours after a light breakfast. This would certainly exclude the possibility of the hormonal therapy producing a latent diabetes. A transient myopia occurs very rarely after the administration of drugs like arsenicals or sulfonamides. This change of refraction is believed to be caused by a sensitivity resulting in a ciliary spasm. It has also been reported in diseases accompanied by severe loss of fluids, such as typhoid or dysentery; it has the same metabolic basis of a disturbed salt-water balance as that occurring in diabetes.

While the corticosteroids exert a powerful influence on the electrolyte balance, the patient under consideration had only a relatively small amount of the hormones and did not show any other signs of water retention. Signs of water retention have become well known early in the history of hormonal therapy, but no changes of refraction have ever, to my knowledge, been reported. It may be that patients receiving corticotropin or cortisone are usually too sick to notice a change in their refraction.

The other possibility—that a toxic disturbance of the centers regulating the tonus of the ciliary body was responsible for the increase of refraction—is even less acceptable, because contact dermatitis is a very common occurrence and no change of refraction has ever been reported in such cases.

This case, then, is presented without diagnosis or explanation. It would be interesting to know whether others have made similar observations without publishing them.

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Submitted for publication Aug. 22, 1955.

Annual Reviews

NEURO-OPHTHALMOLOGY

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Visual Pathways
- Flicker and Standard Perimetry
- Black-Light Perimetry
- Quinine Amaurosis
- Vascular Anatomy of Optic Nerve
- Temporal Arteritis
- Opticomalacia
- Carcinomatosis of the Meninges
- Visual Instability in Multiple Sclerosis
- Spinal Cord Tumor Simulated by Neuromyelitis Optica
- Retrobulbar Neuritis, Uveitis, and Glaucoma
- Retrobulbar Neuritis in Infectious Mononucleosis
- Treatment of Optic Neuritis
- Occult Meningiomas
- Differential Diagnosis of Optic Neuritis
- Embryology of Optic Chiasm
- Ocular Signs in Temporal and Occipital Lobe Tumors
- Bilateral Homonymous Hemianopia
- Diagnosis of Malingering
- The Visual Fields: A Monograph

Higher Visual Disorders
- Balint's Syndrome
- Visual Hallucinations of Self Psychogenic Ocular Symptoms

Papilledema and Increased Intracranial Pressure
- Intracranial Hypertension Without Localizing Signs
- Lumbar Puncture in Patients With Brain Tumor
- Craniosynostosis

Motility and Lids
- Etiology of Ophthalmoplegias
- Unilateral Palsy of Elevation
- Myasthenia Gravis
- Convergence Center Myth
- Divergence Palsy
- Centering of Eyes
- Hemifacial Spasm

Nystagmus
- Platybasia and Arnold-Chiari Malformations
- Spasmus Nutans
- Optokinetic Nystagmus

Pupils
- Pupillography in Topical Diagnosis
- Herpes Zoster Ophthalmicus
- Unilateral Argyll Robertson Pupil

Ocular Signs in Vascular Diseases
- Syringomyelia
- Carotid Artery - Cavernous Sinus Fistula
- Collateral Circulation Through Ophthalmic Artery

Brain Tumors
- Ocular Signs as Earliest Signs of Brain Tumors

Ocular Complications in Neurosurgery
- Unilateral Blindness

Books

THE NEURO-OPHTHALMIC literature is large but most papers present nothing new. Instead of preparing brief abstracts and an interminable bibliography, I have preferred to be selective and devote the space to significant articles. The most valuable papers to appear in the past year are those on the anatomy of the vascular supply of the optic nerve by François, Neetens, and Collette, the visual fields by Brodie Hughes, the convergence center by Warwick, and pupillography in topical diagnosis by Lowenstein.

Submitted for publication July 1, 1955.

From the Institute of Ophthalmology, Presbyterian Hospital.

VISUAL PATHWAYS

Flicker and Standard Perimetry.—Havener and Henderson [1] studied 90 patients with both flicker fusion and standard perimetric methods to determine the comparative value of these two methods. Not all patients showed field defects. Information of equal value was obtained from both types of perimetry in 66 patients. Superior information was obtained from flicker fields in eight patients and from standard perimetry in nine patients. The authors draw these conclusions: 1. Standard perimetry is the superior method in detecting a very small scotoma, as that caused by a small localized chorioretinal

lesion or by a small lesion in the optic radiation or visual cortex. The flicker bulb is several centimeters in size and is seen by the adjacent normal visual units and therefore fails to reveal a small scotoma. Of course, flicker fields will reveal scotomata and hemianopic defects if they are larger than the bulb. 2. Flicker fields are superior in detecting minimal depressions of the central area in retrobulbar neuritis. The authors frequently found that subsiding central scotomata are no longer demonstrable by standard perimetry but are still revealed by flicker fusion methods. This implies that retrobulbar neuritis is a widespread disorder and affects enough of the macular fibers and adjacent fibers to involve a central area larger than the size of the flicker bulb. A patient with only a 2-degree central scotoma to 1 : 1000 white may show a more widespread depression to flicker. 3. In certain respects flicker fields are too sensitive in that they often reveal depressions in conditions such as pneumonia, toxemia, hypertension, cataract, and so on. In such instances the flicker field defect is of less diagnostic significance than is a depression found by standard perimetry. 4. Flicker testing on the tangent screen shares the same limitations of ordinary tangent screen methods, that is, the inability to detect the far peripheral defects, such as temporal crescent defects, annular scotomata, peripheral constriction, and defects due to peripheral chorioretinitis, tumor, and retinal detachment.

Some readers may feel that these few cases are without stastistical significance, but one should regard this paper as a valuable contribution because the true value of flicker fields can be judged finally only by additional similar studies. The future will probably teach us that it is not a matter of superiority of one method over the other but that each method has its merits in the detection of certain types of defects, and that the two methods are complementary rather than competitive.

Black-Light Perimetry.—The patient who complains of visual impairment, in the presence of 20/20 acuity and no central scotoma demonstrable with the 1 : 2000 white stimulus, is a diagnostic challenge. Harrington and Hoyt [2] report their success in detecting a central scotoma in this situation by the use of ultraviolet radiation and luminescent monochromatic blue test objects under partially scotopic conditions. The scotopic peripheral retina is many times more sensitive to blue than to red or white, whereas the scotopic fovea is more sensitive to red and white and is less sensitive to blue. In fact, there is a physiological central scotoma for the 1 : 2000 blue stimulus, which the authors demonstrated in 20 normal persons. They conclude that a central scotoma elicited with the 5 : 2000 blue stimulus is definitely pathological. Eighteen cases are reported to demonstrate the value of this techinque in the detection of early and minimal impairments of conduction in lesions of the retina and optic nerve. In most of the visual fields there was a central scotoma for 5 : 2000 blue.

Although I have not had experience with this technique, there are several points to discuss. 1. The fixation object was a 5 mm. white. This size is too large and can produce two types of erroneous results: (*a*) The fixation object may be larger than the scotoma itself (for example, a scotoma for 1 : 2000 white), and thereby the examiner fails to detect a true scotoma that exists; (*b*) the small 1 mm. test object will have to be brought out beyond the periphery of the fixation object before it is recognized, and thus it may appear to the examiner that this represents a central scotoma, whereas a scotoma does not actually exist. 2. The authors state that the patient cannot identify the blue color in this method but simply reports when the test object appears and disappears. I do not understand, therefore, how the patient can be expected to see a 5 mm. blue test object (which does not appear blue), or a 1 mm. white test object, superimposed upon a 5 mm. white fixation object. 3. In comparing their method with a standard tangent screen method, the authors do not state the details of the "standard" method, the size of the fixation object used, nor do

they compare the use of blue in the partially scotopic eye with the use of red test objects in the photopic eye. 4. Finally, the reader should note that in the visual field of the right eye in their Case 6 (Fig. 9) and of the left eye in their Case 18 (Fig. 21) the scotoma for 1 mm. white is larger than is the scotoma for 5 mm. blue!

Quinine Amaurosis.—Drance [3] reports the case of a 20-year-old woman who had the sudden onset of blindness one-half hour after an episode of vomiting. There was no light perception in either eye, the pupils were dilated and did not react to light, and the fundi were normal in all details. Aside from vomiting, the clinical features would justify the diagnosis of acute retrobulbar neuritis. Physical examination revealed an enlarged uterus, and the patient finally confessed she had taken ½ oz. (15 gm.) of quinine as an abortifacient. In six days the vision improved to 20/30 O. U. For 10 days the fundi and retinal vessels appeared normal, but on the 11th day the discs became pale and the retinal arterioles became constricted. One month after the onset of blindness the acuity was 20/15 in each eye with some irregular depressions of the visual fields. The case illustrates that in quinine amaurosis the fundi and retinal vessels may maintain normal appearances for as long as 10 days.

Vascular Anatomy of Optic Nerve.—Modern drugs have decreased the incidence of optic nerve diseases due to syphilis and other infections, but the increase in the human life span has increased the incidence of optic nerve involvements due to vascular diseases. It is necessary that we know more about the finer anatomy of the blood supply of the entire visual pathway. A significant contribution in the past year has been the work on the vascularization of the lamina cribrosa and optic nerve by François and Neetens.[4]

A detailed review of the literature presents the status of conflicting opinions. The authors injected 34 specimens with Neoprene latex 572 by Ashton's technique and dissected the vascular network under the binocular microscope before and after fixation in 10% formol. They emphasize that the anatomical conceptions deduced experimentally are strongly supported by embryological and comparative anatomical studies. The original paper should be consulted, but it is worth while to summarize the important conclusions.

1. It is commonly believed that the only source of blood supply to the optic nerve is from the internal carotid artery via the ophthalmic artery. François and Neetens, however, state that the ophthalmic artery is not the only vessel supplying the optic nerve. Anastomoses between the lacrimal artery and the middle meningeal artery, and others derived from the external carotid system, and from the arterial circle of Willis, also supply the optic nerve.

2. It is frequently written that the central retinal artery itself supplies the optic nerve, and also that this artery anastomoses with the arterial circle of Zinn-Haller at the level of the lamina cribrosa. In contrast, the authors maintain that the central retinal artery supplies only retinal tissues; it does not send branches to supply the optic nerve, and it does not anastomose with the circle of Zinn-Haller at the lamina cribrosa.

3. Early in its course the ophthalmic artery gives off a central optic nerve artery, which enters the optic nerve posterior to the entrance of the central retinal artery. This central optic nerve artery passes to the center (axial core) of the optic nerve and divides into a posterior branch, extending to the optic canal level, and an anterior branch, extending to the optic disc. These branches and their capillaries supply the axial macular nerve fibers (centrifugal system). The capillaries of the anterior branch may serve additionally as vasa vasorum for the central retinal artery. Also, the anterior branches of the central optic nerve artery anastomose with the arterial circle of Zinn-Haller and supply the optic nerve head.

4. Capillaries issuing from the network of the pia mater over the length of the optic nerve supply the peripheral nerve fibers (centripetal system). These arise from nu-

merous anastomoses between the extra-orbital cerebral vessels.

François, Neetens, and Collette [6] studied the anatomy of the vascular supply of the optic nerve by the technique of micro-arteriography. After the injection of Heyden Thorotrast into the optic nerve vessels, microangiograms were made of horizontal and transverse histological sections. The illustrations are beautiful, and their descriptions should be read. The authors found two basic types of vascular units: (*a*) The transverse units are in the form of a pentagon, and encircle the nerve fiber bundles as complete or incomplete rings over the entire length of the optic nerve; (*b*) the longitudinal units pass in the interfascicular spaces in an anteroposterior direction. These build up the pentagonal units. Collateral vessels branching from these two vascular units create an inextricable meshwork of capillaries which anastomose most intimately. The central artery and central vein receive their nutrition from these two vascular units, whose nutritive branches are often mistaken for collaterals of the central retinal artery. The authors emphasize that such collaterals do not exist, and that the central artery supplies only the retina, and perhaps the papilla, but does not supply the optic nerve.

Temporal Arteritis.—In the past 20 years numerous authors have reported loss of vision associated with temporal arteritis (cranial arteritis; giant-cell arteritis). Since the ocular manifestations are not generally appreciated, it is well that further papers continue to appear. A recent excellent description of the condition is given by Meadows.[8] The patients are usually over 55 years of age. After an initial period of malaise and slight fever, severe pains develop in the temporal or occipital region on one or both sides. The scalp is tender, and the temporal or occipital arteries are tender to palpation. About 25% of these patients lose the vision in one or both eyes, due to acute ischemia of the optic nerve or retina. Pathologically, the media is destroyed and infiltrated with giant cells, lymphocytes, and polymorphonuclear leucocytes. The intima is grossly thickened. The lumen is reduced to a slit.

Examination should direct attention to the history of pain, state of the temporal arteries, loss of vision, and the fundus appearances.

Pain in one or both temporal or occipital regions, lasting from a few days to a few months before the loss of vision, is frequent. It is important to know that the pain may be slight or absent in some cases of visual loss.

At some stage of the disease the temporal arteries may be swollen, tortuous, nodular, and tender. Pulsation is usually diminished or absent. An apparently normal pulsating artery does not necessarily exclude this diagnosis, for in some cases biopsy of the artery reveals the characteristic pathological changes.

Premonitory visual symptoms often occur a day or so before the visual loss. The loss of vision is rapid, occurring within two hours to two days. Both eyes are usually involved, the second eye losing its vision either simultaneously or within a few days after the visual loss in the first eye. The prognosis is characteristically poor. The patients usually remain blind; infrequently, slight improvement occurs.

The fundus appearances are interesting. In most of the author's patients the visual loss was out of proportion to the fundus changes. The findings were limited to slight or moderate papilledema with a few small hemorrhages. This incongruity between fundus changes and severe visual loss may lead to a mistaken diagnosis of retrobulbar neuritis; furthermore, the fundus picture is not that of occlusion of the central retinal artery. Weeks later, optic atrophy ensues.

The differential diagnosis includes occlusion of the central retinal artery, retrobulbar neuritis, cortical blindness, and brain tumor. The picture of central arterial occlusion is uncommon in temporal arteritis. Retrobulbar neuritis may be mistakenly diagnosed, but the age of the patient is against the diagnosis of multiple sclerosis and is in favor of the diagnosis of ischemic disease. The bilateral

loss of vision, loss of pupillary reactions, disc edema, and subsequent optic atrophy are characteristic of optic disc and retinal lesions, and not of cortical blindness. In the early stages, the history of head pain associated with optic disc edema may suggest brain tumor; in the later stages the history of head pain and the presence of optic atrophy also suggest brain tumor.

The prominent features in the recognition of this condition include the head pains, tender temporal arteries, rapid loss of vision in both eyes, disc edema, and increased sedimentation rate, occurring in a person over 55 years of age. In the later stages, blindness with optic atrophy, and diminution or absence of pulsation in the temporal arteries are diagnostic. Biopsy of the temporal artery may prove the diagnosis and also provide striking relief of pain due to the severance of the sensory nerves. Treatment to date has been ineffective.

I regard the renewed interest in the microscopic anatomy of the vascular supply of the optic nerve and disc, exemplified by the papers of François, Neetens, and Collette, as of paramount importance in the advances which will lead to an understanding of the type of blindness occurring in association with temporal arteritis and other systemic vascular diseases, which produce an acute or chronic ischemia of the cross section of the optic nerve at the level of the optic disc. It is interesting, therefore, that Meadows [6] suggests that the visual loss in temporal arteritis may be due to involvement of the short ciliary arteries as they take part in the formation of the arterial circle of Zinn at the nerve head. This could well account for the severe loss of vision accompanied by only slight blurring of the discs.

Opticomalacia.—This clinical picture of loss of vision associated with temporal arteritis is described by Kreibig,[7] who refers to it as opticomalacia. He reports a case in which giant-cell arteritis of both ophthalmic arteries and both temporal arteries was found 15 days after the onset of bilateral loss of vision. A malacic area, 1.5 mm. in diameter, with complete necrosis was found posterior to the lamina cribrosa. He relates seven similar cases. In those without clinical temporal arteritis the diagnosis was proved by biopsy of the temporal arteries. The author stresses that in some cases the process spares the temporal arteries and involves only the ophthalmic arteries.

Carcinomatosis of the Meninges.—Severe headaches and rapid loss of vision occurring in women over 55 years of age were the main features of three patients reported by Fischer-Williams, Bosanquet, and Daniel.[8] Tenderness of the scalp was so marked in one case that the diagnosis of temporal arteritis was strongly considered. Later, multiple cranial nerve palsies developed. Lumbar puncture revealed carcinoma cells in the spinal fluid. Necropsy revealed primary bronchial carcinoma in two cases and primary adenocarcinoma of the colon in the third case. Grossly the brains appeared essentially normal; a slight thickening of the meninges could easily have passed unnoticed. Microscopically, however, there was widespread carcinomatosis of the meninges without the presence of a tumorous deposit in the brain tissue. There was a thin sheet of cells, often in a single layer, on both the arachnoidal and pial surfaces of the subarachnoid space. The optic nerves were completely surrounded by a sheet of tumor cells, which penetrated along the blood vessels somewhat into the nerves; the nerves showed severe degenerative changes. A comparison of these three patients with the case reports in the literature suggests that this condition, although rare, is a distinct clinical and pathological entity. It is worth keeping in mind in the differential diagnosis of temporal arteritis with bilateral loss of vision.

Visual Instability in Multiple Sclerosis.—Patients with multiple sclerosis note fluctuations in their symptoms under certain circumstances. For example, they are more comfortable in cold than in hot weather. Heat can aggravate existing symptoms or induce new ones; an example is the transient

visual impairment occurring after a hot bath. Edmund and Fog[9] report the case of a 25-year-old male student who noticed visual impairment following physical exertions, such as taking short walks. Their case records revealed that 44 of 152 patients (25%) had similar transient visual impairment in connection with excessive heat or physical exertion. Experimentally, the authors subjected 45 patients to a hot-air bath of 55 C for 25 minutes, and compared their symptoms with those of normal persons and with patients harboring other neurological diseases, also exposed to the same experimental conditions. In a significant majority, symptoms and signs—nystagmus, ataxia, facial palsy, bulbar signs, pareses of the extremities, reflexes, sensory disturbances, visual impairment, ocular muscle palsies—were increased or induced by this heating procedure in the multiple sclerosis group. The exacerbations occurred within 15 minutes and subsided within 20 minutes after the heating was discontinued. Fifteen of the forty-five patients developed transient visual impairment. No relationship was found between this transitory impairment and optic nerve lesions. The authors hypothesize that the visual impairment is due to transitory myopia resulting from edema of the lens capsule, but their evidence for this theory is extremely weak.

Spinal Cord Tumor Simulated by Neuromyelitis Optica.—Acute spinal cord syndromes associated with acute bilateral optic neuritis justify the diagnosis of neuromyelitis optica. Acute bilateral optic neuritis without spinal cord signs does not justify this diagnosis but should be regarded as probably the primary manifestation of the disease, in which the spinal cord symptoms may develop later; cases of acute bilateral optic neuritis which never develop spinal cord signs are regarded by some authors as abortive types of neuromyelitis optica. On the other hand, acute spinal cord symptoms without optic neuritis lead to diagnostic difficulties. Markham and Otenasek[10] report a most unusual case. A 29-year-old man developed acute spinal cord symptoms. Myelography demonstrated a complete subarachnoid block at the level of C 6. This suggested a hemorrhage into a neoplasm. A cervicodorsal laminectomy revealed intense swelling of the spinal cord due to acute myelitis. The true diagnosis of neuromyelitis optica was not established until three months later, when an exacerbation of myelitis occurred, accompanied by simultaneous acute bilateral optic neuritis. The authors have found only one other case in the literature, reported by Silbermann,[11] in which a complete spinal subarachnoid block due to myelitis was found by myelography.

Retrobulbar Neuritis, Uveitis, and Glaucoma.—Cohen and Chamlin[12] report the case of a 27-year-old man with a history of sudden onset of blurring of vision in the left eye. The most likely diagnosis was primary uveitis with secondary glaucoma, and retrobulbar neuritis secondary to the uveitis. They advise that a slit-lamp examination be done in all cases of optic neuritis to determine if it is associated with uveitis.

Retrobulbar Neuritis in Infectious Mononucleosis.—Papillitis due to infectious mononucleosis has been reported, but Schecter, Lipsius, and Rasansky[13] relate what they consider to be the first reported case of retrobulbar neuritis as a complication of infectious mononucleosis. The vision in the right eye of a 6-year-old boy became blurred four weeks after the onset of his illness. The fundi were normal. After several months the vision gradually returned to normal.

Treatment of Optic Neuritis.—Kazdan and Kennedy[14] selected for treatment 22 patients who were thought not to have a demyelinizing disease as the cause of their optic neuritis. Eleven patients were treated with intravenous corticotropin, and eleven patients were treated with intravenous killed typhoid bacilli. The results revealed no superiority of one method over the other as regards duration of symptoms and the degree of visual recovery.

Occult Meningiomas.—Birge and Whitcomb[15] report three cases of suprasellar

meningioma with severe visual impairment as the main clinical sign. They emphasize that early diagnosis is the responsibility of the ophthalmologist, who must study the visual fields carefully and urge the neurologist to perform contrast x-ray studies if the tumor is to be removed before irreparable visual damage has occurred. Judging from the advanced stages of severe visual loss in their cases, it seems that the word "occult" is hardly appropriate.

Differential Diagnosis of Optic Neuritis.—Chamlin [16] discusses the differential diagnosis of optic neuritis, which includes papillitis and retrobulbar neuritis. The differential diagnosis of papillitis includes papilledema due to increased intracranial pressure, pseudoneuritis, drusen of the optic disc, juxtapapillary chorioretinitis, and vascular neuroretinopathy. The differential diagnosis of retrobulbar neuritis includes toxic amblyopia, central angiospastic retinopathy, intrinsic tumor of the optic nerve or chiasm, and intracranial mass lesion compressing the optic nerve or chiasm. Closure of the central retinal artery or one of its branches is listed in the differential diagnosis, but discussion of this important condition has been omitted from the text. This paper is valuable because it presents one ophthalmologist's opinions, based upon his personal experiences with optic nerve diseases.

Embryology of the Optic Chiasm.—Barber, Ronstrom, and Muelling [17] describe the histological sections displayed in their scientific exhibit showing the development of the human optic chiasm and its relations to adjacent structures. In the early stages the anlage of the chiasm occupies a large portion of the floor of the third ventricle, but in the adult only the posterior aspect of the chiasm is related to the ventricle. Hydrocephalus with dilatation of the third ventricle produces pressure which severely compresses the chiasmal fibers in the early stages, but has little harmful effect during the later stages of gestation. This is another example showing that congenital abnormalities are more injurious the earlier they occur in fetal life. This material is also included in the more complete monograph on "Embryology of the Human Eye," by Barber.[18]

Ocular Signs in Temporal and Occipital Lobe Tumors.—In many regions of the brain, lesions produce sufficient neurological signs for clinical diagnosis; the ocular signs are unimportant or may provide only confirmatory evidence. In the "silent" areas, however, neurological signs may be absent in the operable stages; the temporal lobe was long regarded as a silent area, until 1911, when Cushing pointed out the importance of visual field changes in the early recognition of temporal lobe tumors. It is now generally accepted that such tumors commonly produce the homonymous hemianopic types of field defect, but the question arises: Can one differentiate between temporal and occipital lobe tumors on the basis of the visual field defects? No general agreement exists concerning the significance of the absence or presence of field defects, of homonymous hemianopic and quadrantanopic defects, of congruity and incongruity, and of macular sparing and splitting. Further opinions on these questions are welcome, and are expressed in an interesting paper by Edmund,[19] who analyzed 208 cases of verified glioma, comprising 196 temporal and 12 occipital lobe tumors. He purposed to obtain further knowledge of the course of the optic radiations, to evaluate the ocular signs—especially the visual field changes—in localization diagnosis, and to determine if any ocular or neurological signs can be related to the pathological nature of the lesion.

He is in agreement with the majority of investigators, who believe that a dissociation in the optic radiation occurs in the temporal lobe, as described in 1907 by Meyer. As is well known, this concept states that the most dorsal fibers continue straight posteriorly to the occipital lobe in the angle between the temporal horn and the main ventricle, whereas the ventral fibers pass anteriorly and downward to sweep around the lateral wall of the temporal horn before proceeding posteriorly to the occipital lobe.

In 196 temporal lobe tumors Edmund found that the commonest symptom is headache and the commonest clinical signs are papilledema and visual field defects. Subjective visual symptoms are rare, but objective ocular signs are common. It is interesting that headache occurred in 75% of patients without papilledema and also in 75% of patients with papilledema. Papilledema occurred in 115 of the patients (60%), but only 28 (24%) of these complained of visual obscurations. A difference in the degree of papilledema in the two eyes is of no value in lateralization of a tumor; this is in agreement with general opinion. Although there is no relation between the incidence of papilledema and the pathological type of tumor, it was found that papilledema was more frequently associated with malignant than with benign neoplasms. This is not due simply to the more infiltrative growth of malignant tumors, but appears to be a consequence of the rate of tumor growth, for the author found that two-thirds of the patients with a history less than 6 months had papilledema, whereas two-thirds of the patients with a history longer than 12 months did not have papilledema.

Of the 196 cases of temporal lobe gliomas visual fields could be studied in 153 (79%)—a high percentage! It is significant, and may appear surprising, that 67 patients (44%) had normal fields. This may be due to the fact that the tumor merely displaces the visual fibers as the compressible ventricle yields ahead of it, thus preventing compression of the visual fibers. Eighty-six patients (56%) had homonymous hemianopic types of defect, as follows:

Homonymous hemianopia		34%
With macular involvement	5%	
With macular sparing	29%	
Superior quadrantanopia		21%
Inferior quadrantanopia		1%

Thus, the most important ocular sign in temporal lobe tumors is a visual field defect.

Authors differ in their experiences regarding the types of field defects caused by temporal and occipital lobe tumors. The reliability of their reports is influenced by two factors: (*a*) The anatomical location of the lesion is less accurate when obtained only from the operative findings, and is more accurate when determined at necropsy, and (*b*) a tumor may arise in the temporal lobe and infiltrate to surrounding regions, or it may arise elsewhere and extend into the temporal lobe. Edmund has wisely selected cases in which the tumors were located solely, or mainly, in the temporal or occipital lobe. To determine whether there is a relation between the visual field defect and tumor location, he divided the temporal lobe tumors into four groups: (*a*) anterior group, anterior to the temporal horn; (*b*) lobar group, in the same area as the temporal horn, (*c*) posterior group, posterior and inferior to the temporal horn, and (*d*) total group, in the entire temporal lobe. On this basis he found that field defects occur in increasing frequency as the tumors are situated more and more posteriorly. Thus, field defects occurred in 25% of the anterior group and in 54% of the posterior group. Also, tumors involving the walls of the ventricle produce field changes more frequently than do tumors without relation to the walls.

Of 12 cases of occipital lobe tumors, fields could be studied in only 9, but all 9 cases showed complete homonymous hemianopia; 4 had macular sparing, and 5 had macular splitting. Although other authors have found normal fields in 5% to 20% of occipital tumors, Edmund found complete hemianopia in 100% of his cases. No instance of quadrantanopia was found in this group.

The author found no relation between the types of field defect and the pathological nature of the lesion. Nor did he find incongruity to be of value in localization.

Surely the time has arrived, on the basis of reliable clinical and pathological studies, when we can discard once and for all the theory of double representation of the macular areas in the visual cortices. Homonymous sparing of the macular area is the result of widespread representation of the homony-

mous halves of the macular areas in the unilateral striate area. Total excision of one occipital lobe produces homonymous hemianopia with macular *splitting*.

Macular sparing, in itself, is not a manifestation of the location of the lesion, but simply represents the degree of involvement of the macular fibers at any level. In other words, either macular sparing or macular splitting can occur in lesions of the optic tract, or optic radiation, or visual cortex. In the anterior part of the temporal lobe the upper and lower visual fibers are spread out and are separated by the intervening macular fibers; in this region, quadrantanopia and macular sparing are common. Somewhat more posteriorly the optic radiation is arranged more compactly; a lesion here produces macular impairment earlier and is less likely to produce quandrantanopia. Still further posteriorly, in the visual cortex, the fibers again spread out over a larger area and the macular fibers are widely represented; here, macular vision is spared until advanced stages of the tumor.

Bilateral Homonymous Hemianopia.—Reese [20] reports 16 cases of bilateral homonymous hemianopia occurring in association with conditions such as anoxia due to respiratory difficulties, ventriculography, vascular obstruction, blood transfusion reaction, and head injury. Varying degrees of visual recovery ensued, although some patients remained blind permanently. The visual impairments are regarded as due to lesions involving the suprachiasmal pathways. Visual field charts are not shown; furthermore, the localization of the lesions were not convincingly suprachiasmal in all the cases. For example, in Case 1 the optic discs became extremely pale. In Case 3 there was edema of the disc and retina in each eye, and in Case 7 the visual loss was in one eye only. The paper serves to remind us again that the visual pathways are vulnerable to nutritional impairment, but it offers little in regard to the exact localization of the lesions.

In cases of bilateral homonymous hemianopia it is uncommon for the right and left homonymous defects to develop simultaneously. Such simultaneously occurring defects have only rarely been attributed to occlusion of the basilar artery, because basilar artery occlusion is rare and is usually fatal. Kearns, Wagener, and Millikan [21] report three patients. Each experienced sudden, simultaneous onset of bilateral homonymous hemianopia, clinically diagnosed as basilar artery occlusion. This diagnosis was confirmed in one case at necropsy, which revealed a thrombus in the basilar artery and infarctions in the pons and in both occipital lobes. This diagnosis is justified in a case of sudden, simultaneous bilateral homonymous hemianopia, when accompanied by brain stem signs, such as internuclear ophthalmoplegia, nystagmus, and long-tract signs. The patients are usually subjectively unaware of their severe visual loss.

Diagnosis of Malingering.—The ophthalmologist occasionally suspects a patient's alleged visual loss in one eye to be functional in nature, and yet finds this difficult to prove. Sproule and Havener [22] employ the tangent screen and frequently have proved the functional nature of unilateral visual loss. Each eye is examined alone on the tangent screen. Then the fields are determined with both eyes open. Functional losses are characterized by changes such as homonymous field loss on the side of the alleged defective eye, or by the inability to demonstrate the previously elicited blind spot in the normal eye, or by loss of the normal field when tested binocularly. Illustrative fields are shown.

The Visual Fields: A Monograph.—It is a pleasure to call attention to the superb monograph on visual fields by Brodie Hughes.[23] It relates his personal experiences and opinions gained from employing the principles and methods of quantitative perimetry in the examinations of thousands of personal cases. All visual fields depicted were determined by the author, who makes the significant statement that "if full benefit

is to be obtained the tests must be carried out by oneself and not delegated to an assistant." Most textbooks of perimetry devote their major attention to field defects produced by strictly ocular diseases and apportion only a small section to neurological diseases. Hughes' book is unique, as it deals primarily with the field defects encountered in neurological and neurosurgical conditions.

The field defects have been correlated with the locations of the pathological lesions observed at operation or at necropsy. Generally, it is believed that field studies are of value only in localization diagnosis, but Hughes cites instances in which the characteristics of the fields suggest the pathological nature of the lesions.

The text is written in a clear, concise, and refreshing style. The bibliographical references have been selected with care. Hughes' construction of the visual island differs from Traquair's classic; it gives a truer concept of the island and more easily explains the mechanism of field depressions. The fields are recorded on the Cushing-Walker type of chart, which is still the most excellent form. Valuable practical suggestions are given for the technique of recording. The isopters have been determined on both the perimeter and tangent screen, enabling one to evaluate each method. One disappointment is that the visual acuity is not stated on the field charts.

Regarding Meyer's loop, Hughes concludes that, although there is some forward looping of the ventral fibers, it is probable that they do not extend as far anteriorly as the tip of the temporal horn. This conclusion is supported by cases in which no field defects resulted following excisions of the tip of the normal temporal lobe as performed for psychomotor epilepsy and for gaining access to middle fossa lesions.

The book should immediately establish itself as a classic and is a most welcome addition to neuro-ophthalmic literature.

HIGHER VISUAL DISORDERS

Balint's Syndrome.—Hécaen and de Ajuriaguerra [34] report three cases of the syndrome described in 1909 by Balint. It is characterized by three features: (*a*) Psychic paralysis of visual fixation. "Psychic" is used in the sense that ocular motility is normal when higher psychological functions are not involved. Two phases are distinguished. First, the inability to look toward a point in the peripheral visual field; this wandering of visual fixation in search of the object is followed by the second phase, of secondary fixation once the object has been met by chance. The most striking feature is the inability to shift from a point of fixation. This locking, or spasm, of fixation, as an isolated symptom, is fairly common but is a secondary, and not a primary, disturbance. (*b*) Optic ataxia. Tests reveal the inability of the patient to execute coordinated voluntary movements in response to visual stimuli. For example, the patient extends his hand in the wrong direction when attempting to grasp an object; by slow, cautious, disjointed movements the hand finally touches the object. This is in contrast to the tabetic, who partly corrects his ataxia when permitted to employ his sight instead of his defective proprioception, whereas in Balint's syndrome the inability to control movements visually is aided by proprioceptive control. (*c*) Disturbance of visual attention. Attention is normal for nonvisual stimuli, but there is general impairment of attention for visual stimuli. Although the absolute visual field is normal, only the most prominent stimuli reaching the macula are seen by the patient. For example, a patient may see the tip of his cigarette but not the flame of the nearby match.

Hécaen and de Ajuriaguerra consider their three cases to be instances of Balint's syndrome; the characteristic features are not marked, but are sufficiently distinct to differentiate the cases from those of simple spasmodic fixation. From their cases and others in the literature the authors believe that Balint's syndrome, even in its minor form, indicates that the lesion is bilateral, and that it constantly involves the parieto-occipital regions. Necropsy revealed bilat-

eral parieto-occipital lesions in two of their cases. It is interesting that in their non-necropsied case the visual fields showed a defect encroaching deeply on the midline from both superior and inferior extremities of the vertical meridian, but sparing foveal vision. This defect is typical of a bilateral occipital lesion, interhemispheric, as was pointed out in 1954 by Dubois-Poulsen and Magis.[26]

Cogan and Adams [26] point out that Balint's syndrome and ocular motor apraxia described by them in 1953 [27] are probably one and the same syndrome; this would bring the total number of reported cases of this entity to 10 of the acquired variety and 4 of the congenital variety.[28]

Visual Hallucinations of Self.—Autoscopy, or hallucinations of one's self, is uncommon. Dewhurst and Pearson [29] report three cases in association with organic brain lesions. A 46-year-old man had a subarchnoid hemorrhage complicating malignant hypertension. His "double" image appeared solid, as if it were a mirror image, and usually repeated the actions of the patient. At night the image would undress and lie down in the next room. It never said anything, however. The patient was well aware that this was only a hallucination, but it had persisted so constantly that the patient drew up a chair for his image when he visited his physician. A 62-year-old man had a glioblastoma in the left temporo-parietal region, revealed by biopsy. Three weeks later the patient saw images of himself "as if looking in a mirror." A 57-year-old man developed autoscopy 13 years after a piece of shrapnel had lodged in his right temporal lobe. The theoretical mechanisms are discussed, and the authors suggest that autoscopic hallucinations occur only in persons with a highly developed visual memory sense of their corporal being.

Psychogenic Ocular Symptoms.—Gifford [30] emphasizes that a knowledge of psychiatry is necessary and of immense value to any physician, and defends this advice by citing interesting stories culled from nonmedical literature. The self-destruction of vision is related in the myths of Oedipus, Noah, Lady Godiva, and in the Gospel according to St. Matthew. Hysterical blindness, psychosomatic ocular diseases, and other ophthalmic manifestations provide interesting reading.

PAPILLEDEMA AND INCREASED INTRACRANIAL PRESSURE

Intracranial Hypertension Without Localizing Signs.—The ophthalmologist, neurologist, and neurosurgeon occasionally encounter a patient with papilledema and increased intracranial pressure, but without localizing neurological signs. The ophthalmologist fulfills his obligation by excluding simulating conditions, such as papillitis, juxtapapillary choroiditis, drusen of the optic discs, and pseudopapilledema; he should know that true papilledema can occur without localizing neurological signs. The condition is frequently referred to as "serous meningitis."

Berg, Rosomoff, Aronson, Silbermann, and Pool [31] surveyed 2000 cases in which ventriculography and/or craniotomy had been performed for suspected intracranial tumors; 238 of these had increased intracranial pressure (evidenced by papilledema or cerebrospinal fluid pressure over 250 mm. of water) without localizing signs. The final diagnoses were arranged in four groups:

(*a*) Lateralized mass lesions were revealed in 117, or 49%, of the cases; 99 were supratentorial, and 18 were cerebellar.

(*b*) Midline obstructive lesions involving the third and fourth ventricles were found in 62, or 26%, of the cases.

(*c*) Miscellaneous lesions accounted for 32, or 14%, of the cases; 8 included hypertension, hypoparathyroidism, and tuberculous and Cysticercus meningitis. No diagnosis was possible in 24 cases.

(*d*) Intracranial hypertension of unknown cause ("serous meningitis") accounted for 27, or 11%, of the cases. Nineteen were young females; three had venography which revealed no evidence of thrombosis of the superior longitudinal sinus.

Thus, the authors discovered lateralized mass lesions or midline obstructive lesions in 75% of their cases of increased intracranial pressure without localizing signs—by employing ventriculography and craniotomy. This is an excellent illustration of the necessity for complete investigation in these cases, despite the negative clinical examination; it also exemplifies the competition the ancillary methods of examination are offering to the clinical examination.

Another excellent paper on this subject is that of Foley,[32] who reviews the literature and analyzes his personal cases. Since the advent of ventriculography the syndrome has been defined more precisely, based upon the cardinal radiological finding of a normal ventricular system. His criteria for the diagnosis of "benign intracranial hypertension" include (*a*) headaches and visual obscurations, which are common complaints; (*b*) intact cerebration; (*c*) bilateral papilledema; (*d*) no localizing neurological signs; (*e*) no systemic hypertension or other systemic diseases which can produce papilledema; (*f*) objective evidence of increased intracranial pressure (other than papilledema), such as increased lumbar puncture pressure, radiological signs of increased pressure, or high dural tension at the time of ventriculography; (*g*) cerebrospinal fluid of normal composition but under increased pressure, and (*h*) normal ventriculograms.

Various names given to this syndrome include serous meningitis, pseudotumor cerebri, tumor equivalent, toxic hydrocephalus, otitic hydrocephalus, hypertensive meningeal hydrops, intracranial pressure without tumor, and so on.

Thrombophlebitis of the dural sinuses is commonly cited as the cause of this syndrome; such cases have been termed "otitic hydrocephalus." In an analysis of 46 cases from the literature, Foley concluded that there is no satisfactory evidence that mural thrombophlebitis of the superior longitudinal sinus is responsible. The data do suggest, however, that thrombosis of the lateral sinus is the important factor, although this alone does not produce the syndrome. In addition, the lateral sinus involved must be the major sinus; also there must be cerebral edema. The term "hydrocephalus" is erroneous, since the ventricles are normal, or even smaller than normal, in size.

It is significant that prolonged intracranial hypertension with a normal ventricular system occurs more commonly without than with a history of otitis media. Sixty nonotitic cases in the literature were also analyzed by the author and found to present general features similar to those of the otitic cases except that the nonotitic type occurs principally in females, usually in their early teens or early 20's. Numerous causes have been suggested but none have been proved. Vision tends to fail earlier in this type than in papilledema due to brain tumor. There is little, if any, evidence to suggest that dural sinus thrombosis is responsible. The deep subarachnoid space found at craniotomy is an artefact; therefore, the term "meningeal hydrops" is incorrect.

Foley divided his 60 personally observed cases in three groups:

(*a*) The otitic type, in which thrombosis of the major lateral sinus is the probable cause: 11 cases.

(*b*) The type following mild infections and mild head injuries, affecting young males and females equally: 16 cases.

(*c*) A larger group, without a history of infection or injury, occurring almost exclusively in women, particularly in the fourth decade: 31 cases.

The syndrome subsides after one month to three years. The frequent visual impairment ensuing in this condition will be discussed by the author in a later paper.

Zuidema and Cohen[33] review the records of 80 patients with this syndrome of "pseudotumor cerebri" and classify them in three groups: (*a*) Those with actual brain tumor but in whom the tumor is not yet revealed by existing methods of diagnosis; the correct diagnosis is made only by conscientious follow-up during the next several months. (*b*) Those with dural sinus thrombosis,

usually associated with an upper respiratory infection; dural sinus venography may provide helpful information in diagnosis in the future. (*c*) The remaining patients have "idiopathic" intracranial hypertension, and follow-up observations reveal that their long-time prognosis is good. The authors emphasize that this diagnosis should be one of exclusion, and be made only after exhaustive diagnostic procedures have been done.

Lumbar Puncture in Patients with Brain Tumor.—To determine the frequency of untoward reactions in patients with brain tumor on whom a lumbar puncture had been performed, Lubic and Marotta [34] reviewed 401 cases of histologically verified brain tumors in which lumbar puncture had been performed prior to air studies, arteriography, or surgery. Only one patient showed evidence indicating an untoward effect (death) of the puncture. It is difficult to understand their figures. They found obvious papilledema in 46, or 12%, of the cases. However, 127 patients (32%) showed increased intracranial pressure (over 190 mm. of water); 33 of these 127 cases had obvious papilledema. From this it appears that 94 patients (23%) harboring brain tumors had increased intracranial pressure without papilledema! The authors imply that lumbar puncture in the presence of increased intracranial pressure is not as dangerous as is generally believed, and that it should be done if knowledge of the composition of the spinal fluid will contribute to the differential diagnosis. It appears that, if lumbar puncture is truly dangerous in the presence of increased intracranial pressure, the optic discs are poor indicators of this risk, since 100 of their patients (25%) had elevated pressure without obvious papilledema.

Craniosynostosis.—Advances in the neurosurgical treatment of craniosynostosis have resulted in increasing alertness in the detection of these cases in the early stages, when surgical intervention can be effective in relieving the increased intracranial pressure, thereby preserving vision and other cerebral functions. Cases of premature closure of the cranial sutures have been reported in siblings and in successive generations in families but such reports are few. French and Suechting [35] report two cases, a brother and a sister, to emphasize the possible familial occurrence of this deformity. It is interesting that the diagnosis was made in the 6-week-old girl because the mother insisted that x-rays be taken, since the older son had had the same condition.

MOTILITY AND LIDS

Etiology of Ophthalmoplegias.—Rucker [36] presents an interesting analysis of 282 cases of ophthalmoplegia. It is consoling to read that the cause was not determined in 25% of the patients. Eighteen per cent were due to head injuries; 19% were attributed to occlusive vascular disease, as evidenced by the presence of hypertension or arteriosclerosis; a few had diabetes. Seven per cent were third nerve palsies due to aneurysms of the circle of Willis. In ophthalmoplegia due to brain tumor the sixth nerve was the most frequently affected nerve; uncommonly did brain tumor cause third or fourth nerve palsy. Multiple sclerosis was the cause of sixth nerve palsies in 4% of the cases; in no patient did it affect the third or fourth nerve.

Unilateral Palsy of Elevation.—An interesting condition is that of palsy of elevation of one eye, with or without ptosis. These cases are usually considered to be congenital in origin, and nuclear or infranuclear in type, but they may be acquired and supranuclear in type, as described by Bielschowsky.[37] More recently, Balbran and Norbis [38] report 10 cases of unilateral paralysis of the elevators (superior rectus and inferior oblique muscles) considered to be of the supranuclear type. For anatomical reasons, a nuclear lesion is unlikely, since this would require the lesion to affect selectively only the portions of the third nucleus complex corresponding to the superior rectus and inferior oblique muscles, without affecting the remainder of the complex. An infra-

nuclear lesion is unlikely, since this would require selective involvement of nerve fibers supplying only these two elevator muscles. An orbital lesion is improbable, since the fibers innervating the superior rectus muscle pass with those supplying the levator muscle in the superior division of the third nerve, and the fibers innervating the inferior oblique pass along with those supplying the inferior rectus, medial rectus, sphincter, and ciliary muscles in the inferior division. On the other hand, clinical evidence supports a supranuclear localization. Voluntary, command, and attraction movements are paralyzed, but a positive Bell's phenomenon is present: The examiner, as he separates the eyelids at the same time that he requests the patient to close his eyes, observes an upward deviation of the apparently paralyzed eye. This phenomenon proves the integrity of the peripheral neurone from the nucleus to the muscle. A positive Bell's phenomenon was observed in 8 of the 10 cases.

The age of onset varied from birth to 3 years in seven cases, in which one must conjecture whether the palsy was congenital or acquired. The authors report, however, three cases of acquired paralysis occurring at ages 12, 39, and 40 years. This demonstrates that this condition is not always congenital! Furthermore, in most cases the lid droops to follow the hypotropia of the affected eye, producing the manifestation of a pseudoptosis. Frequently, this pseudoptosis is mistaken for a true ptosis, and the elevator palsy is overlooked.

Myasthenia Gravis. — Numerous papers have been published in the past several years concerning new drugs employed in the diagnosis and treatment of myasthenia gravis. A few have been selected to bring the ophthalmologist up-to-date on the present status of the subject.

In 1950 MacFarlane, Pelikan, and Unna [39] first reported the beneficial effect of the intravenous use of edrophonium (Tensilon) chloride in a child with myasthenia gravis. Tensilon is 3-hydroxyphenyl-dimethylethylammonium chloride, and is one of the quaternary ammonium salts shown to exert a direct stimulatory effect on the neuromuscular junction. It is more potent at this junction than it is at other cholinergic sites and is therefore unaccompanied by undesirable cholinergic effects.

In 1952 Osserman and Kaplan [40] described a new diagnostic test for myasthenia gravis, consisting of the intravenous administration of 1 cc. (10 mg.) of edrophonium chloride. Increase in muscular strength and elevation of the ptotic eyelids occurred rapidly, often within 30 seconds, and usually within 2 minutes. The drug is of little value in treatment, since its effects are transitory, due to its rapid excretion.

Westerberg, Magee, and Shideman [41] in 1953 found edrophonium to be effective in alleviating myasthenic symptoms, but its transitory effect limited its value in daily treatment. Oral ingestion is also ineffective. In 1947 pyridostigmine, or Mestinon, was reported. Westerberg and Magee [42] evaluated this drug in 22 patients. Twenty-one of the patients preferred pyridostigmine to neostigmine because the duration of its beneficial effects was longer, and particularly because the muscular strength was maintained on an even level without the necessity of frequent rest periods to regain strength. Another advantage was its decreased toxicity and absence of muscarinic effects.

Boruchoff and Goldberg [43] call the attention of ophthalmologists to the use of edrophonium in diagnosis and report the case of a 17-year-old boy who had ptosis and paralysis of the lateral and medial rectus muscles of each eye. The test with neostigmine (Prostigmin) was equivocal. Within one minute after the intravenous injection of 1 cc. (10 mg.) of edrophonium chloride the patient could raise his eyelids and the muscle movements were normal except for persistent paralysis of the left medial rectus muscle. The effect disappeared after five minutes.

Convergence Center Myth.—Duke-Elder [44] states, "A center for convergence is universally admitted and the assumption of

Brouwer (1918) that this is situated in Perlia's nucleus is generally accepted."

Those of us who are repulsed by the concept of "centers" for functions in the brain welcome the refreshing and excellently written paper by Warwick,[45] who attacks the concept of a center for convergence with the blows it so well deserves. The paper should be required reading and is one of the finest contributions to neuro-ophthalmologic literature in the past year.

In 1899 Perlia and Bruce independently described a median group of cells between the right and left oculomotor nuclei, but neither attributed any specific function to it. In 1891 Knies initiated the idea that Perlia's nucleus is a mediating center for convergence. In 1918 Brouwer concluded that Perlia's nucleus is characteristic only of animals capable of binocular vision. His scheme of the oculomotor nucleus complex was criticized in 1926 by LeGros Clark, who contrasted the absence of Perlia's nucleus in some primates having binocular vision with its exuberance in other mammals not possessing binocular vision. In 1943 Crosby and Henderson had difficulty in distinguishing a nucleus of Perlia in man or monkey. Despite these and numerous other criticisms, the convergence nucleus, anatomically and functionally, persists as a feature in standard neurological and ophthalmological literature.

Warwick examined several hundred sections of each midbrain of 100 monkeys, 2 chimpanzees, and 3 humans and some human fetal brains to provide topographical and experimental data.

Topographical study of the histology of the third nucleus complex showed that the median nucleus of Perlia is usually absent in the monkey and confirmed the poor development of this feature in the chimpanzee and man, despite the possession of binocular function in all three forms.

Experimental observations were based upon the study of midbrains of 95 monkeys in which various branches of the oculomotor nerve were severed in the intracranial and intraorbital cavities. Extirpation of the medial rectus muscle, to determine the locus of its motor pool, regularly produced retrograde degeneration in the ipsilateral oculomotor nucleus; the changes were confined to the ventral subdivision, and in no case were they observed in the paramedian groups or any other part of the oculomotor complex.

The experiments revealed that when a central nucleus of Perlia does exist its nerve cells are not internuncial and therefore cannot constitute an integrative center. In the monkey, the cells contribute fibers to the third nerve, but they innervate the superior rectus muscle, and to a lower degree the inferior oblique muscle, and do not innervate the medial rectus muscle. Previous studies by Warwick in 1953 showed that the nerve cells innervating the superior rectus muscle are located in the paramedian zone of the contralateral oculomotor nucleus, and the main motor pool of the inferior oblique lies in the lateral oculomotor mass.

Regarding the parasympathetic pathways, ciliary ganglionectomy did not produce changes in the central nucleus of Perlia, and lesions of the preganglionic axones produced changes only in the Edinger-Westphal and anteromedian nuclei; these are distinct from Perlia's central nucleus.

In an exciting discussion, Warwick denounces the elaborate array of "centers" invented to explain ocular motor abnormalities. Pathological and clinical evidence for such centers has never been convincing. The custom of regarding ocular motions as occurring in geometrical directions, performed by the yoking of pairs of muscles, is oversimplified. All 12 extraocular muscles participate simultaneously, though in varying degrees, in any binocular movement. The rapidity of movement, the complexities of variations in tension in each muscle, and the precision with which conjugate, convergent, divergent, and torsional movements are performed cannot conceivably be controlled by simple centers. The delicacies of binocular vision are learned after birth, with use and experience, and are perfected in partnership with the development of vision. It is reasonable, therefore, to believe that

ocular motility is organized, at least in part, at cerebral levels and not alone on nuclear midbrain levels.

It is also curious that convergence has been singled out from the rest of binocular activity and assigned a center. Even if such a center does exist, it must be subservient to cerebral influences, and in this sense a convergence center assumes even a smaller role as an initiator of eye movements. Furthermore, it is difficult to understand why a median, unpaired midbrain center for control of a bilateral function should be postulated for convergence, and yet not for other bilaterally organized functions, such as mastication, walking, speech, and the like; Broca's area, though unpaired, is at a cortical level. (There are no centers for gaze up and to the right, gaze down and to the left, and so on.)

The term "nucleus of convergence" signifies a degree of integration and of mutual control of fine synergy which cannot be expected from a group of lower motor neurones and is contrary to neurological precept. As Warwick states [45]:

> To look therefore at mesencephalic levels alone for a supposedly autonomous centre controlling convergence, which may justly be regarded as the ultimate perfection of binocular movement, is basically unphysiological. It seems that we have in the convergence centre a notion originally conceived on meagre grounds and perpetuated with little critical evaluation of its implications. By its superficial attractiveness, and the nebulous terms in which it is usually framed, this hypothesis has evaded the onslaught of much adverse criticism, to survive as an interesting example of neurological mythology.

He concludes that the central nucleus of Perlia cannot be considered a "center" for convergence in any meanings of the word. In view of his data, and those of previous workers, the author concludes that "little basis remains for further perpetuation of this old and ill-conceived idea."

Divergence Palsy.—Divergence insufficiency (or, better, divergence palsy) is discussed in an informative paper by Lyle.[46] Subjectively, the only symptom is the sudden onset of diplopia for distance; single vision is present in the reading range. A thorough examination of the ocular movements is essential to arrive at the correct diagnosis. This condition must be differentiated from convergence spasm, unilateral or bilateral abducens nerve palsy, internuclear ophthalmoplegia, myasthenia gravis, ocular myopathies, and thyrotoxic ophthalmoplegia. Divergence palsy can be caused by a variety of pathological lesions—traumatic, viral, vascular, neoplastic, and toxic—involving the midbrain or pons. The causative lesion should be treated, of course, but the ophthalmologist can help the patient temporarily or permanently by prescribing Grab-Front prisms, base out, to be worn for distance only, or bifocals with the prismatic corrections in the upper segments only. Occasionally it is necessary to resect the lateral rectus muscles. Five typical cases are described.

Centering of Eyes.—Conventional classifications of the binocular movements seldom mention one type of action, namely, the centering of the eyes to the midposition regardless of the location of the globes prior to the movement. This midpositioning phenomenon, or centering of the eyes, is discussed in an intriguing paper by Bender, Teng, and Weinstein [47] on the basis of experiments performed by stimulating various parts of the brains of cats and monkeys with the Horsley-Clarke stereotaxic technique.

Ocular midpositioning results from stimulation of many areas close to the midline, in the paramedian zone, in the diencephalon, mesencephalon, pons, medulla, and in many portions of the cerebellum, and in portions of the frontal and occipital cerebral regions. The authors believe that the phenomenon should be interpreted as a patterned conjugate eye movement, as the horizontal and vertical conjugate movements are regarded. If this is so, interesting questions arise. How would irritative or paralytic states of this midpositioning function be manifested? Perhaps the attacks of staring and eye centering observed in petit mal represent the irritative manifestation. How would paralysis

of the eye-centering function manifest itself? Perhaps the ocular divergence or drifting observed in sleep, anesthesia, and coma is due to lack of eye centering. Another possibility is the unilateral or bilateral nystagmus occurring on forward gaze; this condition has never yet been explained.

Hemifacial Spasm.—Greear [48] reviews the literature on hemifacial spasm and reports two cases and his treatment of them. Hemifacial spasms may be caused by many central nervous system lesions or may follow recovery from facial paralysis, but in most cases the cause is unknown. These primary hemifacial spasms occur only in adults and are usually unilateral; they are irregular and intermittent, almost always involve the eyelids, and at the height of the attack all the muscles of one side of the face are in either a clonic or a tonic state of contraction. The patient feels no compulsion to make the movement, is unable to prevent or stop the spasms voluntarily, and cannot reproduce them voluntarily. The spasms may persist in sleep, thus differing from a tic. The condition is so distressing and disabling that the patient (as Lyle states in his discussion of this paper) is willing to exchange facial paralysis for his spasms. Various treatments have been tried for this long-recognized condition. Greear had success in two patients treated by this method of injecting alcohol into the parotid plexus; the needle enters 1 cm. posterior to the area employed by O'Brien for producing temporary akinesia during cataract surgery.

NYSTAGMUS

Platybasia and the Arnold-Chiari Malformations.—In the past two decades increasing interest has been given to platybasia and the Arnold-Chiari deformity. Cogan and Barrows [49] report nine cases in detail and emphasize that ophthalmologists should be acquainted with these conditions, since the ocular manifestations may be the presenting complaints, or may simulate other conditions, such as multiple sclerosis, tumor of the brain stem or cerebellum, and other posterior cranial fossa lesions.

Platybasia consists of an upward bulge of the occiput in the region of the foramen magnum; the upper cervical vertebrae may be partially fused to each other and to the skull, with a protrusion of the odontoid process of the axis into the posterior cranial fossa. The Arnold-Chiari deformity consists in a herniation of the cerebellar tonsils and medulla through the foramen magnum; meningomyelocele and spina bifida are frequently but not invariably associated. The symptoms and signs are similar in both conditions and are due partly to direct involvement of the cervical nerves and partly to compression or traction on the brain stem and cerebellum. Indeed, the two conditions often coexist. The common symptoms include disturbances of gait, headache, stiff neck, numbness and weakness in the extremities, and blurring of vision. These may be precipitated or exaggerated in severity by coughing, sneezing, or turning of the head. A "bull-neck" or hunched-up appearance should suggest platybasia; spina bifida or meningomyelocele should suggest the Arnold-Chiari deformity.

Skew deviation and asymmetry of the opticokinetic response were observed in some patients; but the one ocular sign observed in all patients is nystagmus. It was characteristically of the jerk type, being horizontal on looking to either side and vertical on looking upward or downward. Horizontal nystagmus may occur with lesions in many parts of the central nervous system, and vertical nystagmus practically always indicates a lesion of the posterior cranial fossa; however, the type of the nystagmus offers no clue in any case to the type of the responsible lesion.

Platybasia can be suspected, but not definitely diagnosed, from the clinical signs alone; final diagnosis depends upon the x-ray studies, which reveal the pathognomonic arching of the occiput and the high position of the odontoid process. The most instructive point emphasized by the authors is that in several patients the routine skull x-rays were reported as normal; the true diagnosis

was revealed only when special x-rays were taken specifically for visualization of the foramen magnum region. This is an excellent example of the apparently paradoxical values of clinical signs versus x-ray studies. The diagnosis cannot be made from the clinical signs alone but depends upon the x-ray studies; and yet the roentgenologist may fail to detect the lesion unless he is directed to take the proper views by the alert clinician, who suspects the possibility of these conditions on the basis of the nonpathognomonic nystagmus.

Phillips [50] discusses some fine points concerned in the radiological diagnosis of these cases and summarizes briefly the clinical manifestations in 20 patients.

Spasmus Nutans.—Spasmus nutans is a rare but well-known triad consisting of nystagmus, head nodding, and anomalous head positions; its onset occurs between the ages of 6 months and 3 years. The literature states that recovery occurs spontaneously in 3 to 12 months. Norton and Cogan [51] reexamined 20 patients two years or more after the onset of the condition and found that the duration may be much longer than is generally thought. In two patients, for example, the signs were still present after eight years. They emphasize that the fineness and the asymmetry of the nystagmus in the two eyes are sufficiently characteristic that one can diagnose this syndrome even in the absence of head nodding and head turning. The infants had all been reared under adequate lighting conditions. Visual acuity was normal.

Optokinetic Nystagmus. — Carmichael, Dix, and Hallpike [52] studied 73 patients with unilateral supratentorial lesions to determine the cerebral nervous mechanisms responsible for directional preponderance to the side of the lesion of caloric and optokinetic nystagmus. The details are too lengthy to summarize satisfactorily, but the paper is recommended to the interested reader. Briefly, the authors conclude that the directional control of caloric and optokinetic nystagmus is normally effected through independent nervous mechanisms situated respectively in the posterior parts of the temporal lobes and in the supramarginal and angular gyri.

The literature on optokinetic nystagmus through 1947 is reviewed by Roelofs,[53] but the article is too long to be abstracted.

PUPILS

Pupillography in Topical Diagnosis.—In the past 15 years several excellent papers by Lowenstein have appeared in the American literature describing the technique and diagnostic values of his system of pupillography. They are packed with facts, clearly stated and logically proved, concerning the characteristics of the normal and pathological pupillary reflexes. The information is most amazing and requires us to change many of our traditional concepts (or misconcepts) which are so carelessly copied from one textbook to another. Since three important papers on pupillography appeared during the past year, it is most appropriate to call attention to some of the previous articles * and to recommend that they be studied slowly and carefully; the material is of fascinating interest to the physiologist but is of even greater practical value to the ophthalmologist and neurologist.

As Lowenstein emphasizes, the clinical examination of the pupils as performed by most neurologists and ophthalmologists is limited to noting their shape, size, equality, and reactions to light and in near vision. Difficulties are encountered due to the smallness of the pupils, the rapidity of their motions, the impossibility of observing both pupils simultaneously for comparison, and the variations in size and reactivity from moment to moment. Our usual examinations are crude and unreliable, and detect only gross abnormalities in the pupillary states and reflexes. Sympathetic and parasympathetic, central and peripheral, excitatory and inhibitory influences are active simultane-

* References 54 to 61. Reference 54 has bibliographic references from 1920 to 1940.

ously in varying degrees; upon this constantly shifting equilibrium are superimposed the various reflexes. Obviously, these subtle movements escape ordinary clinical observations, and are captured only by the accurate and objective recordings of pupillography.

The subject is too detailed and complex to abstract in its entirety and can be understood only by a study of the original papers. To excite interest in this pursuit, I shall cite a few observations from Lowenstein's papers which expose several traditional misconceptions.

1. Physiological Anisocoria: Contrary to general opinion, anisocoria is never physiological. Although it may be due to a harmless condition, it always indicates unilateral or asymmetrical bilateral pathological lesions.

2. Unilateral Amaurotic Mydriasis: It is commonly believed that impairment of vision or blindness in one eye, due to disease of the retina or optic nerve, produces homolateral mydriasis, and that a lesion of the anterior two-thirds of the optic tract produces contralateral mydriasis. This belief is due mainly to the writings of Behr, so commonly quoted in standard books. Lowenstein [92] proves that anisocoria does not occur in man in cases of a lesion of the first neuron: This term applies to the ganglion cell layer and its axones, which pass through the retina, optic nerve, optic chiasm, and optic tract. Such lesions produce a quantitative reduction, or loss, of the direct and consensual reflexes to light and to darkness; stimulation by light of standard intensity produces "low-intensity" reactions; in darkness the pupils are of normal size, but in diffuse illumination they are larger than average; the normal triphasic pattern of the reflex to darkness is changed into a biphasic pattern, and the reactions to near vision are normal, if sufficient vision exists to perform the test. Thus, at any instant, the two pupils are equal in size; there is no anisocoria.

(*a*) In incomplete lesions of the optic nerve, stimulation of this homolateral eye produces low-intensity reactions in both pupils; stimulation of the normal eye produces fully developed reflexes of equal extent in both pupils. In unilateral blindness, neither pupil reacts when light stimulates the blind eye, whereas both pupils react equally when the seeing eye is stimulated. There is no anisocoria. The term unilateral amaurotic mydriasis is erroneous.

It is interesting that low-intensity reactions may be present although vision is restored following a previous impairment; the reverse may be seen, in which the pupillary reactions are fully preserved although vision is severely damaged. These phenomena are observed, for instance in retrobulbar neuritis due to multiple sclerosis.

(*b*) In lesions of the optic chiasm, stimulation of the right eye produces low-intensity reactions, equal in amount and alike in shape, bilaterally; stimulation of the left eye also produces the same type of reaction. Depending upon the location of the lesion within the chiasm, however, impairment of the light reflex may be more pronounced upon stimulation of one eye than of the other.

(*c*) A lesion in the anterior two-thirds of the optic tract also produces low-intensity reactions, equal in the two pupils, when either eye is stimulated. Although the defect may be more pronounced when the right or when the left eye is stimulated, this asymmetry is less common than with lesions of the optic chiasm.

(*d*) Lesions in the posterior third of the optic tract, or in the lateral geniculate body or optic radiation, do not produce pupillary abnormalities. This fact may aid in differentiating a homonymous hemianopia due to a lesion in the anterior tract from a homonymous hemianopia due to a lesion in the anterior radiation, since the hemianopia in either case may be somewhat incongruous.

3. Anisocoria and Additional Lesions: Anisocoria is frequently seen clinically in lesions of the optic nerve, chiasm, or tract. This is not due to a lesion of the first neuron, as already stated, but is caused by involvement of the sympathetic or third nerve fibers in the orbit or intracranial cavity by the same or by a separate lesion. Such neighborhood

signs are common and may be erroneously interpreted as an essential part of the syndrome. For example, some cases of homonymous hemianopia are associated with anisocoria and some are without; the clinical observations may be correct, but the conclusion that the anisocoria is due to the visual pathway lesion is incorrect. It is generally impossible by means of clinical examination to differentiate between the pupillary signs produced by a lesion of the optic nerve, chiasm, or tract and those produced by a lesion of the sympathetic or third nerve pathways; pupillography will provide this differential.

4. Anisocoria Due to Unequal Illumination: Again, it is commonly regarded that the pupil of the eye receiving the stronger illumination constricts more than does the other pupil. Jones,[63] working in Lowenstein's laboratory, demonstrated that it is impossible to produce "physiological anisocoria" by unequal illumination of the eyes in man (and in monkeys). The direct light reflex of the stimulated eye and the consensual reflex of the opposite pupil are exactly equal. Again, misconcepts on this phenomenon are due to Behr, whose error is recopied repeatedly.

5. Dynamic Contraction Anisocoria: In dynamic contraction anisocoria the pupils—equal in size in darkness—become unequal in light. The responsible lesion is somewhere in the parasympathetic reflex arc.

(*a*) If the right pupil, for example, constricts less extensively than the left, regardless of which eye is stimulated, the lesion is somewhere in the efferent pathway, which is composed of the third neuron, of preganglionic fibers from the third nucleus (Westphal-Edinger) to the ciliary ganglion, and of the fourth neuron, of postganglionic short ciliary fibers to the iris sphincter.

(*b*) Another type of dynamic contraction anisocoria is that in which unequal illumination causes a greater miosis in the stimulated eye than in the opposite eye. Lowenstein describes this syndrome of "alternating contraction anisocoria" in another excellent paper.[64] In this condition the pupil of the stimulated eye contracts more extensively than does the consensually reacting pupil of the opposite eye. This may be unilateral, in which the pupils become unequal when one eye is stimulated but remain equal when the other eye is stimulated, or bilateral, in which the direct reaction of the stimulated eye always exceeds the consensual reaction of the other eye. The author presents a brilliant analysis of the possible locations for the responsible lesions. Since first neuron lesions cannot produce anisocoria, and since third and fourth neuron lesions cannot produce the alternating phenomenon, it remained to consider the possibility that the lesion is in the second neuron. Further analysis showed that the lesions limited to the second afferent neuron alone cannot produce the alternating syndrome. The author then tabulated the 100 theoretically possible combinations of lesions involving both the first and the second afferent neurons and found that there are only two pairs which can produce the unilateral syndrome and only two pairs which can produce the bilateral syndrome. Furthermore, only one of each of these two pairs is likely to occur pathologically. He concludes that the lesion involves both the right and left crossed second neurons in the posterior commissure, plus the first neuron in one (unilateral syndrome) or both (bilateral syndrome) brachia of the superior colliculi.

This syndrome was found in 158 (23%) of 690 cases; two-thirds were unilateral and one-third were bilateral. It is observed in specific and nonspecific central nervous system infections (35%), multiple sclerosis (11%), vascular diseases (17%) and heredodegenerative conditions (14%).

In a later paper, Lowenstein[65] describes a syndrome which occurs as a sequela of virus infections and consists of excessive general fatigue, increased fatigability, mental depression, mononeuritis or polyneuritis, and the phenomenon of alternating contraction anisocoria. The acute infection may be mild and pass unnoticed, but the alternating contraction anisocoria, in the absence of neurological

signs, is indicative of organic involvement in the pretectal area of the midbrain and serves to differentiate the symptoms from functional states, and from diseases such as Economo's epidemic encephalitis, syphilis, and multiple sclerosis.

A study of this series of papers convinces the careful reader that each pathological shape of the individual components of the various pupillary reflexes indicates damage at specific sites within the neural pathways for pupillary control. It becomes apparent that pupillography is of supreme value in topical diagnosis.

Herpes Zoster Ophthalmicus. — Most authorities believe that the lesion causing the Argyll Robertson pupil is located in the afferent pathways. Naquin [66] reminds us that too little attention is given to the possibility that the lesion may be in the efferent fibers passing from the third nucleus to the iris. Some writers have suggested that there may be two separate efferent pathways, one for the light reflex and one for the near reflex. Naquin agrees with this theory on the basis of the case of a 54-year-old man who had herpes zoster ophthalmicus with kerato-iritis, right; seven years later the vision was 20/15 in each eye. There was atrophy of the right iris; the pupil was small, 1.5 mm. in diameter, and did not react to light directly or consensually. The left pupillary reactions were normal. Both pupils reacted briskly to near vision. The features were those of a unilateral Argyll Robertson pupil; neurosyphilis was excluded. The author believes there are two separate efferent pathways for pupillary constriction, but he fails to explain why the fibers subserving the light reflex are so consistently involved in syphilis and the convergence fibers so consistently spared; nor does he present anatomical evidence for two such fiber pathways.

Unilateral Argyll Robertson Pupil.—With the biomicroscope Apter [67] found unilateral Argyll Robertson pupils in 13 of 46 patients with neurosyphilis. Each miotic, light-rigid pupil was associated with iris abnormalities, such as absence of the collarette, transillumination, and fine radial striations. In a second paper, Apter [68] reviews the literature concerning the theories of the pathogenesis and localization of the lesions producing the Argyll Robertson pupil. She concludes that there is no central nervous system lesion that can possibly produce the complete unilateral Argyll Robertson syndrome, including the miosis, light rigidity, and preservation of reaction to near vision. Her theory is that the miosis and light rigidity are due to abnormalities in the blood vessels, nerves, and muscles in the iris itself, and that the preserved near-vision reaction is simply the result of the forward movement of the root of the iris when the ciliary muscle contracts. She concludes that all evidence is incompatible with the theory of a central nervous system localization of the lesion.

OCULAR SIGNS IN VASCULAR DISEASES

Syringomyelia. — Yourish, Wollin, and Nathaniel [69] report a case of syringomyelia and syringobulbia with unusual ocular signs. The bulbar conjunctival and episcleral veins were dilated, tortuous, and numerous in both eyes; the arteries appeared normal. In the right fundus the retinal veins were very dilated and tortuous; a dilated saccular aneurysm arose from the superior temporal artery. The left fundus was normal. The authors believe these ocular changes have never been described previously. In view of the recent neurological literature, which reveals an increasing recognition of vascular neoplasms and malformations as a common cause of syringomyelia, it appears justified to believe that the vascular anomalies in the eyes of this patient are strong evidence that similar vascular malformations exist in the cervical and bulbar regions.

Carotid Artery-Cavernous Sinus Fistula. —Yaskin and Spaeth [70] report the case of a 65-year-old woman who was injured in an auto accident. Proptosis, conjunctival congestion, and sixth nerve paralysis developed bilaterally. A bruit was audible over the entire skull. A right carotid arteriogram

revealed a carotid artery-cavernous sinus communication on the right side. Complete recovery ensued, with disappearance of all symptoms and signs, following ligations of the right common carotid artery and the right internal carotid artery. The case is reported because of the rarity of bilateral sixth nerve paralysis in this condition. Yaskin assumes that the abducens nerve paralyses were due to compression of the nerves by the dilated cavernous sinuses, but Spaeth remarks that it is difficult to explain how both six nerves were involved.

Tamler [71] reports the case of an 86-year-old man who showed the classical signs of carotid artery-cavernous sinus communication on the contralateral (left) side only. At autopsy the fistula was found on the right side. The author believes that the absence of signs on the homolateral side can occur if there is a thrombosis of the ophthalmic vein leading from the sinus, or if the internal carotid artery blocks the egress of blood from the sinus by a ball-valve mechanism. The reader should note, however, that the earliest signs in this patient were on the homolateral (right) side, and therefore the clinical signs were actually bilateral, and were not solely contralateral.

Collateral Circulation Through Ophthalmic Artery.—It is well known that anastomotic connections exist between the external and internal carotid arteries by way of the ophthalmic artery. Arteriographic confirmation of this fact is reported by Vaernet,[72] who relates four cases of thrombosis of the internal carotid artery in the neck; arteriography revealed filling of the carotid siphon and intracranial vessels. This filling occurred by way of the ophthalmic artery through anastomoses with the external carotid arterial system. The author stresses the importance of the ophthalmic artery in supplying collateral circulation to the brain in cases of occlusion of the internal carotid artery and, on the basis of this, argues against the occasional advice of some neurosurgeons to ligate the external carotid artery in an attempt to increase circulation to the brain.

Taveras, Mount, and Friedenberg [73] report arteriographic demonstration of anastomotic circulation between the internal and external carotid arteries by way of the ophthalmic artery in five cases following ligation of the internal carotid artery in the neck for intracranial aneurysms and in six cases of spontaneous thrombosis of the extracerebral portion of the internal carotid artery. They now regard filling of the ophthalmic artery as a reliable sign of thrombosis of the internal carotid artery, as opposed to the possible error of injecting the opaque contrast medium into the arterial wall.

BRAIN TUMORS

Ocular Signs as Earliest Signs of Brain Tumors.—The literature provides many discussions concerning the ocular manifestations observed in patients harboring brain tumors, but these papers have usually come from surveys of the brain tumor material of a neurological department. In contrast with this approach, O'Rourke and Schlezinger [74] describe the ocular manifestations observed in 100 eye patients whose initial complaints were strictly ocular and who were first seen by an ophthalmologist and subsequently referred to the neurological service. Thus, they relate the types of ocular symptoms and signs, and the types of brain tumors, that the ophthalmologist is likely to encounter in practice.

The commonest presenting symptom was subjective impairment of vision (84%). Fifty-eight per cent showed an acuity below 20/200 in one or both eyes; 69% had visual field defects, the prechiasmal and chiasmal types being commoner than the hemianopic types. Optic atrophy and/or papilledema was observed in 80% of the cases. Only 17% had diplopia. It is apparent that symptoms and signs due to impairment of the visual pathways, as evidenced by changes in the acuity, fields, and optic discs, are much commoner than are those due to lesions of the motor pathways.

Surprisingly, almost 80% of the tumors comprise only five major groups: pituitary

adenoma, 24%, and craniopharyngioma, 5%; parasellar meningiomas, 21%; metastatic carcinoma of nasopharynx, 10%; cerebellar gliomas, 10%, and acoustic neurinomas, 8%. Thus, 60% involve the parasellar regions and include the pituitary tumors, craniopharyngiomas, meningiomas, and nasopharyngeal metastases. Helpful points in suspecting the pituitary tumors are the frequent evidences of endocrine dysfunction, manifested as amenorrhea in the female and as loss of libido and reduction in shaving frequency in the male. Diabetes insipidus is common in craniopharyngiomas. Careful examination of the cranial nerves and of the nasopharynx may reveal signs indicative of other tumors, such as the meningiomas, acoustic neurinomas, and nasopharyngeal carcinomas.

OCULAR COMPLICATIONS IN NEUROSURGERY

Unilateral Blindness.—Hollenhorst, Svein, and Benoit [78] report that unilateral blindness occurred in eight patients during general anesthesia for suboccipital or posterior cervical operations. The blindness was due to retinal ischemia; varying degrees of orbital edema with ophthalmoplegia were noted. Visual recovery varied from full recovery of vision to complete unilateral blindness. From experiments on monkeys the authors believe the retinal ischemia is due to pressure of the headrest on ocular structures; lowering of blood pressure may be a factor. It should be noted, however, that blood pressures were normal in their Cases 2 and 7.

This report is a valuable warning to neurosurgeons, but it has been known for many years that ischemic blindness can occur if excessive pressure is applied to the eye, as evidenced by reports of cases in which a pressure bandage applied to the eye precipitated or caused blindness. It seems, therefore, that these neurosurgical cases are simply examples of another method of applying excessive pressure to the eyeball. It is reasonable to state that the harmful effect of the pressure will be severer in the presence of hypotension, as is induced, for example, by hexamethonium.

BOOKS

The second edition of "Neuro-Ophthalmology," by Donald J. Lyle,[76] has been greatly enlarged but otherwise maintains its general organization. The particularly valuable features are the photographs of pathological lesions and the composite presentations of important syndromes having significant ocular signs.

The three-volume set on "Clinical Neurology," written by numerous contributors but edited by A. B. Baker,[77] contains an excellent chapter on neuro-ophthalmology by H. P. Wagener and C. W. Rucker.

A second edition of the classic "Neurology" by S. A. K. Wilson has been revised by A. N. Bruce [78] and provides an excellent reference work for details of neurological diseases. The bibliography is arranged most inconveniently, at the end of the book, instead of being placed at the end of each chapter.

"Embryology of the Human Eye," by A. N. Barber,[18] and "The Visual Fields," by Brodie Hughes,[23] have already been mentioned.

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Correspondence

CELLOIDIN AS AN EMBEDDING MEDIUM

To the Editor:—The wholesale condemnation of celloidin as an embedding medium for ocular tissues by Wexler and Richardson, in their article entitled "Paraffin Method of Embedding Ocular Specimens for Microscopic Study," published in the March, 1955, issue of the ARCHIVES, page 365, will surprise workers using the modern rapid methods of embedding in nitrocellulose. The statement that celloidin causes more shrinkage than paraffin is contrary to the experience of workers in delicate zoological and botanical tissues. Shrinkage of the choroid in celloidin blocks is due to poor choice of fixative, formalin being one of the worst offenders. For routine work six hours' fixation in fresh Zenker's solution is ample.

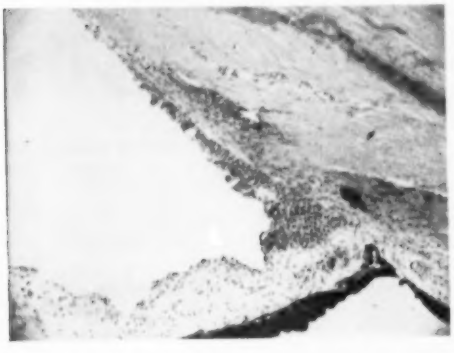

Fig. 1.—Filtration angle in ring melanoma of the iris. Zenker's fluid (six hours); Ehrlich's alum-hematoxylin.

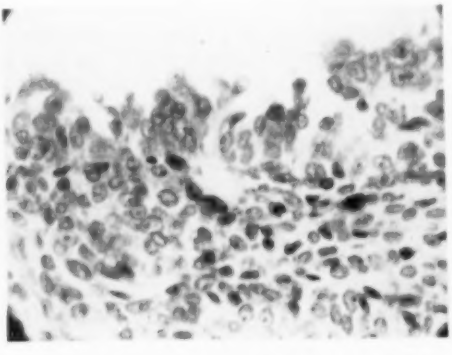

Fig. 2.—Anterior surface of the iris in ring melanoma. Zenker's fluid (six hours); Ehrlich's alum-hematoxylin.

Unfortunately, the belief dies hard that it takes many days or weeks to fix an eye. Small pieces of iris need only half an hour. There is little shrinkage, and 20 minutes in a good alum-hematoxylin stain gives excellent differentiation.

With the methods of Walls (Hot Celloidin Technique for Animal Tissue, *Stain Technol.* **7**:135, 1932) or of Koneff and Lyons (Koneff, A. A., and Lyons, W. R.: Rapid Embedding with Hot Low-Viscosity Nitrocellulose, *Stain Technol.* **12**:57, 1937), the embedding time for a whole eye can be reduced to 36 hours, and with small blocks, to 2 hours. A firm block of uniform density cuts easily at 10μ with the whole eye, and at 6μ with biopsy specimens of iris tissue. Cellular detail is easy to follow, and the vividness with which intraocular structure stands out when stained with Mallory's connective-tissue method makes teaching easy. Without undue haste, sections of the whole eye can be prepared in less than four days after removal of the eye, and biopsy tissue of the iris, in 24 hours.

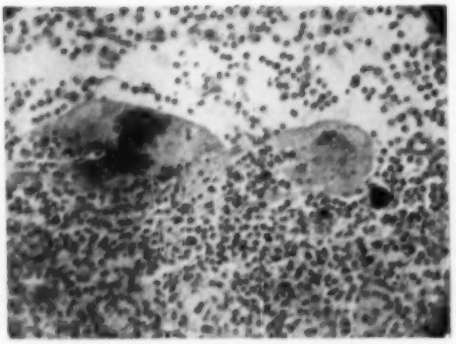

Fig. 3.—Exudate in anterior chamber of an eye, lost after extracapsular extraction of lens. Zenker's fluid (six hours); Ehrlich's alum-hematoxylin.

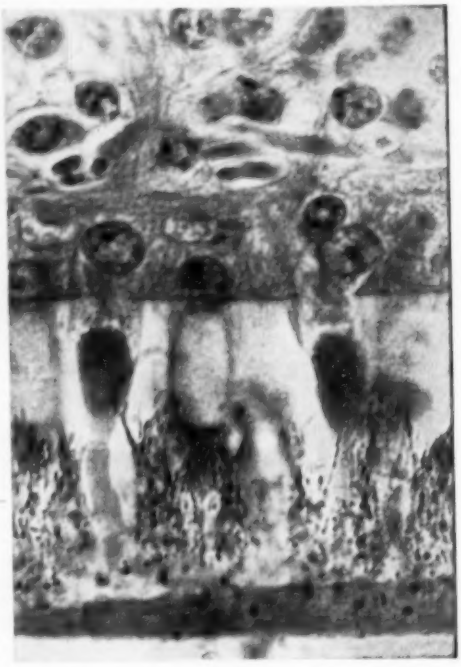

Fig. 4.—Visual cells of Murray turtle (Chelodina longicollis). Kolmer's fixative (24 hours); Heidenhain's iron-hematoxylin.

For many years I did not have the services of a technician, and I was compelled to carry out the whole process of preparation of sections myself. I have always been grateful to American workers for a method which is simple and almost foolproof. I am surprised that it is not used more widely in its country of origin. To round off my defense of celloidin embedding, I am enclosing four photomicrographs taken from routinely prepared sections.

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PERSONAL REQUEST

To the Editor:—As an old subscriber to the ARCHIVES, I would like to publish in the ARCHIVES the following request:

"My son, aged 22, for his behavior and dedication to his university studies, which he is following, has won a prize consisting of a fully paid trip and a two to three months' stay in the United States, thus fulfilling one of his dreams. In order that he may take full advantage of the opportunity and see all that is worth while to be seen in the region or zone which he visits, and above all, get to know the American home life, I should like any colleague who would be willing to receive him into his family circle for, say, 8 to 10 days, to write me with a view to settling details and dates. The boy will travel on or about the middle of next year. He speaks Spanish and German fluently; as far as English is concerned, he manages satisfactorily. For my part, I should be very happy to reciprocate in the event that any member of a colleague's family would like to come out to this country and stay at my home."

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NEW SCLERAL SHORTENING OPERATION

To the Editor:—In the June, 1955, issue of the ARCHIVES, page 865, Dr. William G. Everett reported a new scleral shortening operation consisting in folding the sclera outward and maintaining the fold by mattress sutures in order to shorten the eyeball for the treatment of retinal detachment.

In his article Dr. Everett states that since the preparation of his paper he had learned of a similar operation independently developed by me. This statement is correct. At the same time that Dr. Everett was conducting his experimental and clinical studies on animals and human beings, I was also carrying out the same clinical work. His operation, if not identical, has all the basic characteristics of mine, mainly evacuation of subretinal fluid, folding of the sclera outward, maintaining the fold by mattress sutures, and treating the sclera around the fold by diathermoelectrocoagulations.

Since Dr. Everett reported his new technique, I have developed a new procedure, which, I believe, simplifies further the scleral shortening procedure for the treatment of retinal detachment, using nonrust metal clips instead of nonabsorbable surgical (silk) sutures to hold the sclera. This new procedure will be published in the near future, but, in the meantime, I should like to express my appreciation to Dr. Everett for his kindness of referring to my work in his article.

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VITREOUS CHEMISTRY

To the Editor.—In view of the increasing current interest in the physical chemistry of the vitreous mucoid, it seems desirable to communicate to you a partially completed study made many years ago. Evidence has been reported long since (Friedenwald, J. S., and Stiehler, R. D.: Structure of the Vitreous, ARCH. OPHTH. **14**:789-808, 1935) indicating that the viscosity of the fluid component of the vitreous was largely determined by the presence in that fluid of a small quantity of material of high specific viscosity.

It was found possible to isolate this material as follows: Vitreous fluid was prepared by sucking cow's vitreous through a Buchner funnel without filter paper. The solid matter was removed by centrifugation. To each 100 ml. of fluid 9 gm. of NaCl was added, after which 95% alcohol was added slowly, with manual stirring. At an alcohol concentration of 50%-55% by volume a flocculent precipitate formed, which was separated by centrifugation, washed with alcohol and ether, and dried in vacuo.

The dried material was redissolved in 10% NaCl solution containing 0.25% $NaHCO_3$ in a volume approximately one-fifth that of the original vitreous fluid. A highly viscous, somewhat turbid solution resulted. Alcohol (95%) was added drop by drop, with manual stirring. At an alcohol concentration of 30%-40% the viscosity of the mixture was greatly reduced and centrifugation yielded an almost water-clear supernatant. The precipitate was discarded. Further addition of alcohol up to 55% yielded, again, a flocculent precipitate, which was washed and dried as before.

With successive repetitions of this procedure, the specific viscosity of the product increased as the yield declined. The final yield was 0.7 to 0.8 gm. per liter of cow's vitreous fluid. This material, when dissolved in 1% concentration in isotonic saline solution, resulted in a viscosity nine times that of water. In 0.1% concentration the relative viscosity was 1.8, approximately that of the original vitreous fluid.

The material closely resembled the major mucoid component isolated by a similar procedure from umbilical cord. It gave a positive Molisch reaction for carbohydrate and negative reactions for protein, Ca, and S. The chemical identity of the material was not further studied. The possibility needs to be considered that the procedure used caused condensation of the mucoid into higher and more viscous polymers and that the final product represented an artifact of the treatment. At each stage in the preparation viscosity was tested by dissolving an aliquot of

the product in a volume of isotonic saline equal to the volume of vitreous fluid from which the aliquot was obtained. Successive tests always showed slight losses, never any gains, in viscosity. Moreover, the first isolated sample from the umbilical cord showed a specific viscosity approximately equal to that of the final sample from the vitreous, successive purifications of the umbilical mucoid consisting chiefly in the removal of small traces of proteins. On the other hand, the purification of the vitreous sample involved removal of over 90% of the mucoid originally present. The mucoid fraction discarded, which could be recovered from the original supernatant by precipitation at 85% alcohol, had a specific viscosity of less than 1.3 in 1% concentration dissolved in isotonic saline and was similar to the mucoid fractions of low viscosity isolated from cow's vitreous by other investigators.

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COMMENT ON THE REVIEW OF THE BOOK "REFRACTION AND BODY GROWTH"

To the Editor:—A review on the research memoir "Refraction and Body-Growth" appeared in the March, 1955, issue of the ARCHIVES, page 460. A brief comment on some of the points raised in the review is here presented.

The reviewer refers to the statistically significant differences in refraction between the "Untouchables" and the "Brahmins" presented in the book. The author is inclined to attribute these differences to genetic factors. The reviewer remarks that the author does not enlarge on the dietary difference in the two castes. The author feels that the higher heights in the Untouchables, as compared with the Brahmins, cannot possibly be linked up with malnutrition, which might cause the opposite effect. Myopic trend with higher heights in the Untouchables, therefore, may better be explained by genetic assumption than by any environmental factor, such as diet.

The reviewer states that "the slight excess of myopia found in the girls at the age of 12," as compared with boys, and "the spurt of growth present during the following year" are the data which are "interpreted to correlate rate of growth in weight and height with rate of change toward myopia."

It has clearly been shown in the monograph that there is no relation between myopia and weight. The main evidence on which the statistical relationship between high myopia and height is based is embodied in two tables (XIX and XXVII), which give the values of "*t*" as 2.3069 and 4.2019 for 24 and 22 degrees of freedom, respectively. On page 89 of the book, the author has discussed why this relationship can be believed to be valid. This relationship between high myopia and height is further strengthened by the association of higher heights with myopic trend observed in the Untouchables, as compared with the Brahmins. These data are the main sources of evidence in the relationship of high myopia and height, and not the sex difference at the age of 12. The reviewer has failed to refer to these main sources of evidence which are interpreted to correlate height and high myopia.

On the basis of this main finding, a new hypothesis is developed regarding the relationship of puberty factors in the causation of acceleration of the myopic condition. The relevant data are presented in the chapter on "Puberty and Refraction." There is a frank statement in this chapter of the book (page 71): "The author is perfectly aware that the data in this matter are not enough, nor does he intend to pronounce any inferences which can be raised to the dignity of conclusions. The data, though small, are designed and planned with a view to throw some light on the problems raised in this connection." In the light of the facts given above, a vague remark of the reviewer, "Pendse makes unwarranted conclusions from a relatively small number of cases," appears itself to be unwarranted.

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News and Comment

SOCIETY NEWS

Société Française d'Ophtalmologie.—The 62d meeting of the Society was held in Paris, May 8 through 12, 1955. This was, as usual, a very international gathering and quite a few members from the Western Hemisphere attended: Berens, Dunnington, Daily, Samuels, and Tomassene, from the United States; Brault, from Canada; Pacheco-Luna, from Guatemala; Lech, Busacca, and Moura Brazil do Amaral, from Brazil, and Palomino Dena, from Mexico.

This year the principal paper was on "The Aqueous and Its Physiology" by Marc Amsler, Florian Verrey, and Alfred Huber, of Zurich.

The introduction states that the aqueous should not be considered merely as what fills the anterior chamber, but should be regarded as the interstitial fluid of the whole eye. The aqueous has three roles: regulation of intraocular pressure, metabolism, and reaction to various stresses.

A brief historical sketch starts with the work of Leber, in 1873, and shows that the "modern era" began in 1942 with the discovery of the aqueous veins. Shortly afterward the puncture of the anterior chamber opened new avenues to investigation.

Part I considers the normal aqueous. Chapter I deals with problems relating to intraocular tension, aqueous and laminated veins, trabeculum, Schlemm's canal, intrascleral and episcleral plexuses, and episcleral veins. The origin of aqueous is discussed, as is its output. In Chapter II the metabolic role of the aqueous is considered with the more modern techniques of investigation: microelectrophoresis, chromatography, and isotopes. The importance of ascorbic acid is stressed, as well as that of the electrolytes and bicarbonates. The blood-aqueous barrier is discussed.

Part II deals with the pathological aqueous. Chapter I considers the secondary aqueous which forms after puncture of the anterior chamber. Chapter II is devoted to this puncture: technique, indications, reactions of the eye, intracameral injections. Chapter III is a study of the inflammatory aqueous. Chapter IV considers the biomicroscopy of the aqueous. Chapter V deals with the fluorescein test and its clinical significance.

This very important study of the aqueous will be published in book form toward the end of 1955. It will be obtainable by applying either to the treasurer of the French Society, Dr. Jean Charpentier, 28 rue Vignon, Paris 9e, or to the publisher, Masson & Cie, 120 Boulevard Saint-Germain, Paris 6e.

On Monday, May 9, the papers concerned the retina and uvea. Streiff, Rosselet, and Jequier (Lausanne) reported a case of Romberg's disease (Hemiatrophy of the Face with Uveal Coloboma). Moreau (Lyons) read a paper on the retinal blood pressure in patients with orthostatic hypotension. Changes in the retinal pressure can be observed when no change is noted in the humeral pressure. Miller and Audoueineix (Paris) discussed the effect of chlorpromazine on diastolic retinal blood pressure. Mercier (Tours) has tried chlorpromazine in retrolental fibroplasia or, more exactly, in the early stage of retinopathy, before fibroplasia onset, with indifferent results. Renard and Brégeat (Paris) read a paper on retinal angiomatosis. They described border cases between normal vessels and von Hippel's disease. Charamis (Athens) has used diathermy to coagulate areas of angiomatosis, with good results in early stages. Cuendet, Miescher, Ritter, and Sicard (Lausanne) read a paper on recurrent venous thrombosis in different parts of the body. In some cases the retinal veins are implicated. Valière-Vialeix, Chassaing, Cellier, and Robin (Limoges) observed a retinal tumor which was a true glioma, not a retinoblastoma. Marin-Amat (Madrid) stated his belief that the surgical treatment of retinal detachment was gradually becoming simpler, with better end-results. Bischler (Geneva) described a peculiar aspect of the retina in three patients which she ascribed to Groenblad-Strandberg disease.

On Wednesday, May 11, papers were again on the uvea and retina. Busacca (São Paulo) has examined with a special contact glass the ciliary body in normal

and in abnormal cases. Mawas (Paris) read a paper on the origin, evolution, and histological significance of fixed cells in the iris and the tumors arising from them. Stanković (Belgrade) reported on cases of iritis due to pappataci fever. Sédan and Guillot (Marseilles) have observed an allergic reaction of the anterior uvea to various medications: antitetanus serum, Friedmann's serum, placental implant, and streptomycin. Eoche-Duval, Hervouët, and Lenoir (Nantes) reported on the case of a child with a frontal meningioma and choroidal meningioma. Onfray (Paris) has found that by measuring the width of the retinal arteries and veins one could obtain useful information in cases of uveitis and retinopathy. Jayle (Marseilles) obtained satisfactory results in retinal detachment with a new type of scleral resection in which the sclera is detached and raised, but not removed. Nataf, Besnainou, and Reynon (Tunis) reported excellent results with Paufique's technique of lamellar scleral resection. Ourgaud and Berard (Marseilles) discussed the relationship of retinal detachment and intraocular tension. Odič and Nectoux (Paris) read a paper on the follow-up of 300 cases of retinal reattachment treated surgically and the final result as to working capacity. In their opinion, end-results are less good than is reflected by immediate recovery.

Sunday, May 8, was devoted to "free papers." Bietti, Guerra, and Ferraris (Parma) reported on a study of nodular corneal dystrophy observed in dry tropical countries. Čavka (Sarajevo) has used a sclerocorneoconjunctival transplant (from the cadaver) in symblepharon, with favorable results. François, Rabaey, and Wieme (Ghent) made a study of lens antigens with the technique of electrophoresis on agar. Dupuy-Dutemps and Vergne (Paris) discussed diplopias following operations for squint. Arruga (Barcelona) reported on use of acetazoleamide (Diamox) in glaucoma. Zanén (Brussels) read a paper on the detection of a relative (for color) central scotoma. He demonstrated an instrument for this purpose. Carlevaro (Milan) demonstrated a visual acuity chart which can be used for children and adults.

Thursday, May 12, was also given to "free papers." Trantas (Athens) read a paper on a new type of corneal dystrophy due to local dehydration. Rais (Tunis) discussed corneal transplantation in corneal staphylomas. Barraquer-Moner (Barcelona) reported on his technique of corneal transplantation. He stressed the necessity of numerous (12 to 16) direct sutures. Nordmann and Mandel (Strasbourg) discussed the pathogenesis of alloxan cataract. Viallefont, Boudet, and Montagne (Montpellier) have experimented, in cases of chronic glaucoma, with the effect of sleep induced with chlorpromazine, promethazine (Phenergan), and phenobarbital. The drop in ocular tension, after 10 days, was significant and lasted for some time after the end of the treatment. Larmande, Pestre, and Timsit (Algiers) discussed the various preoperative and postoperative medications for restless patients. Sidi and Mawas (Paris) discussed the cause of lid allergy. They felt this condition was group allergies. Baron (Paris) reported on the diurnal variations of organic and mineral ions in the plasma of chronic glaucoma patients. Jonkers (Gorinchem) reported on the end-results in strabismus of purely orthoptic treatment as against orthoptic-surgical treatment.

During the five-day meeting there were operating sessions and clinical demonstrations in many hospitals. One of the most interesting was that by Dr. E. Zenatti on the electronic tonosphygmo-oscillograph, a new instrument registering the intraocular pressure and the intraocular blood pressure under gradual compression of the eye. This should stimulate promising research.

On Tuesday, May 10, the banquet was held, with Dr. Maggiore, of Genoa presiding, in a boat which cruised up and down the Seine River. The next afternoon an excursion was organized to three castles in the vicinity of Paris: Jossigny, Guermantes, and Champs.

Several other ophthalmological organizations met during the same week: the International Organization Against Trachoma, the Society for Prevention of Blindness, and the Entretiens thérapeutiques. The International Council of Ophthalmology met just before the French Society, on May 7.

The 63d meeting of the Société française d'ophtalmologie will be held in Paris, May 6 to 10, 1956.

EDWARD HARTMANN, M.D.

Books

Modern Trends in Ophthlamology. Third Series. Edited by Arnold Sorsby. Price, $12.50. Pp. 346, including index, with 11 illustrations. Paul B. Hoeber, Inc., 49 E. 33d St., New York 16, 1955.

The third edition of this well-known and useful book suffers from several serious faults. While some of the articles are excellent, others are extremely poor, so that the book is very spotty in caliber; and the editing of several of the manuscripts has evidently been done by someone with no knowledge of the field, so that absurd mistakes have been allowed to appear. That this is the fault of the manuscript editor is attested to by those authors who have been queried by this reviewer, since it seemed obvious that they could not have made such mistakes in their own manuscripts. In Burian and Boeder's article on "Some Newer Aspects of Binocular Vision," for example, the sentence appears as follows: "Attempts to find the distribution of corresponding retinal points by *diopter* determinations are valueless." The word "horopter" was taken out of their original manuscript and "diopter" substituted, probably because the manuscript editor had never heard of horopter and was acquainted with the word diopter. Numerous similar mistakes appear in the same manuscript, including the changing of references so that the discovery of muscle spindles subserving proprioception from the ocular muscles has been attributed to Ludvigh. This is certainly a comedy of errors, since Ludvigh, of all people, still denies that proprioception from the ocular muscles is of any real physiological significance.

The main objection to most of the articles is that they are written by experts on the subject without thought that they are intended for readers not so thoroughly acquainted with the field. If they were, they would already be familiar with the material presented and would therefore not be interested in reading it. Such is the case in many of the articles appearing in Section I, which deals with anatomy, physiology, and optics. Falls' article on the "Diagnostic Criteria of Genetic Affections" is an exception to this, and his article alone is well worth the whole book. It presents in simple, straightforward language the basic facts of genetics, a field which is rapidly becoming more and more important for the practical ophthalmologist. An excellent practical consideration of paralyses of vertically acting muscles is given by Lyle and Cross.

The "Current Aspects of Ocular Pharmacology," by Leopold, and the "Action of X-Rays and Radioactive Substances on Ocular Tissues," by Cogan, are also valuable contributions, which bring these important phases of ophthalmic practice up-to-date. On the other hand, it is hard to see how a book appearing in 1955 could report on recent developments in retrolental fibroplasia and not give anything further about the role of oxygen than the sentence, "However, as yet there is not enough evidence from controlled experiments to establish the relationship between the use of oxygen and the occurrence of retrolental fibroplasia."

It is to be hoped that in future editions greater care will be exercised in keeping the standards of excellence set by the first two volumes, and that the final editing will be done either by the authors themselves or by someone with full knowledge of the field.

Office Procedures. Capt. Paul Williamson (MC), U. S. Army. Price, not given. Pp. 412, including index, with many line drawings, not numbered. W. B. Saunders Company, 218 W. Washington Sq., Philadelphia 5, 1956.

This book is unique. Instead of trying to cover the waterfront and appeal to the medical student, the practicing physician, and the Board-certified specialist,

Dr. Williamson writes for only one group—the general practitioners. For these he offers a practical collection of office procedures based on his own experience. The section on the eye is good. Unfortunately, it is too short; but this is understandable, since the author has to include office procedures for every conceivable condition of the body including psychological testing and roentgenography. It would be well if some day someone would write a book on office procedures in ophthalmology alone just for the general practitioner.

The illustrations are all line drawings, and are not numbered, but each one tells a story in a clear, concise fashion.

Anesthesia in Ophthalmology. By Walter S. Atkinson, M.D. Price, not given. Pp. 90, with 44 illustrations. Charles C Thomas, Publisher, 301 E. Lawrence Ave., Springfield, Ill. 1955.

In this monograph one finds many valuable suggestions on the subject of anesthesia. The need for individualization in preoperative sedation is stressed and correct emphasis placed upon the importance of attention to detail. In a brief summary of "preanesthetic preparation," the author gives an excellent outline of the basic principles involved and calls attention to the necessity for accurate timing and preliminary testing of the sedatives. Akinesia of the orbicularis is discussed fully, and the author's well-known method of blocking the facial nerve is described. The prevention of retrobulbar hemorrhage by the use of a needle with a rounded cutting edge is but one of the many practical suggestions in this text.

The chapter on anesthetic emergencies is particularly worthy of careful study, for in it the results of correct and incorrect treatment are stressed. In discussing general anesthesia he correctly states, "If a well trained anesthesiologist is not available the simplest and safest anesthetic should be chosen." Out of Dr. Atkinson's vast clinical experience and experimental studies has come a most practical manual, which all ophthalmic surgeons will find extremely useful. It is well written, amply illustrated, and clearly printed. The reviewer agrees with the statement that "good anesthesia saves sight" and believes that the author has told us how to secure "good anesthesia."

Keratoplasty. By R. Townley Paton, M.D. Price, $28.50. Pp. 280, with 87 illustrations. The Blakiston Division, McGraw-Hill Book Company, Inc., 330 W. 42d St., New York, 1955.

In this text one finds a very lucid description of every phase of corneal surgery. After an interesting foreword by Dr. Derrick Vail, the author presents his subject in 13 chapters, starting with a historical review and ending with a statistical analysis of his 365 operations. The tribulations of the early operators are related in a factual manner to show the influence they have exerted upon the development of keratoplasty. Von Hippel's suggestion of the need for homoplastic donor material and Filatov's demonstration of the usability of cadaver corneae are listed among the major contributions, as are the improvements in technique suggested by Tudor Thomas, Castroviejo, and others. The chapters on the anatomy and physiology of the cornea are written in simple, easily understandable terms.

The section entitled "Case Selection" contains the bulk of information on the indications for and contraindications to grafting in the various types of corneal disease. To the average ophthalmologist these pages will prove of greatest interest, for in them the author not only gives the opinions of others but also states in clear, concise words his own views and experiences. This chapter is lavishly illustrated with both black and white and Kodachrome "before and after" pictures, which add both to the beauty and to the expense of the volume, without contributing greatly to its scientific value.

In the discussion of donor material, the methods of selection and preservation are given, as well as the legal steps necessary to obtain these corneae. The origin

and functions of The Eye Bank for Sight Restoration are described in detail. The author's operative techniques are given with such clarity that the reader will have no difficulty in following them. In these descriptions are frequent references to the techniques employed by others; yet with characteristic modesty the author unobtrusively states his own preference. The postoperative care and the management of complications are also clearly outlined. In the chapter on radiation therapy no mention is made of the deleterious effects of this form of treatment except to caution against its excessive use preoperatively and to urge care in the handling of the eye postoperatively. The literature on the histology of the healing cornea is incompletely presented, for in the discussion on regeneration of corneal nerves no mention is made of Escapini's investigation on this subject; neither is there any reference to Ashton and Cook's findings on the effect of cortisone on the healing of corneal wounds. To the reviewer, the term "illness of the graft" is vague and undesirable, even though the cause of its clouding often remains unsolved. The concluding statistical summary and tabulated case reports are of great referential value.

The format of this book is excellent. It is clearly printed, and beautifully and profusely illustrated, but its real worth is in its text. It portrays in a most unusual and readable style the vast experiences of the author and contains references to most of the literature pertinent to keratoplasty.

J. A. M. A. Clinical Abstracts of Diagnosis and Treatment. Edited by Noah D. Fabricant, M.D., Price, $5.75. Pp. 670, including index. Grune & Stratton, Inc., 381 Fourth Ave., New York 16, 1955.

This volume is a selection of abstracts published in *The Journal of the American Medical Association* made by Dr. Noah D. Fabricant, Editorial Associate of *The Journal*. According to the editor, the purpose of this selection is "to emphasize two dominant aspects of contemporary clinical practice—Diagnosis and Treatment —the abstracted selections for inclusion in this book are limited to these important fields." It is difficult to judge any except those in the Section on Ophthalmology. It is hard to believe that any ophthalmologist would buy the 13 abstracts listed here when he could obtain them almost as easily in his own *Journal*. The general practitioner might find this book of some use, but here, again, the questionable advantage of having these abstracts bound in one volume instead of retaining them in *The Journal* would have to be balanced against the price of the book. The one advantage which the book does have is an index, but the arrangement of this is such as to make it of very little value.

Receptors and Sensory Perception: A Discussion of Aims, Means, and Results of Electrophysiological Research into the Process of Reception. By Ragnar Granit. Price, $5.00. Pp. 369, with illustrations. Yale University Press, 143 Elm St., New Haven, Conn., 1955.

The rapidity with which the literature on the electrophysiology of the retina has increased in the last few years makes this book a particularly valuable one for those interested in this field. Written by one of the foremost experimenters in electrophysiology, it brings up to date both his own work and that of others in the field since 1947, the date of his previous book, entitled "Sensory Mechanisms of the Retina," published by the Oxford University Press. This volume is not a book for the clinical ophthalmologist, but for those who wish to keep abreast of the important advances in physiology of the retina it can be highly recommended.

The author believes that the impulses which travel up the optic nerve fibers are initiated and kept up by a generator potential of depolarization, which, either directly or by electronic transfer along the fine nerve terminals, depolarizes the nerve. The message which reaches the brain has the character of a simple frequency code. Just how the brain deciphers this code is one of the problems which

Granit attacks. He points out that even from the photoreceptors in the fovea there is not a one-to-one representation in the cortex, and therefore fineness of grain cannot be the only feature which determines visual acuity. He makes use of the fact that the receptive fields in the retina overlap, and he believes that the retina is capable of good discrimination, by using overlapping receptive fields of different sizes, from very large to very small, "the latter likely to be multiplied in cone eyes which have good visual acuity." There is further elaboration of his theory of dominators and modulators, the latter of which determine color vision. There is an excellent bibliography at the end of the book.

CORRECTION

In the article "Outflow of Aqueous Humor: Biomicroscopic Estimation Compared with Tonographic Measurement," by Dr. J. Stepanik and Lt. (jg) R. A. Kemper (MC), U.S.N.R., published in the May, 1954, issue of the ARCHIVES, the formula for the velocity of the projectile (seventh line from the bottom of p. 673) is incorrect. The formula should be $v=l/t$.

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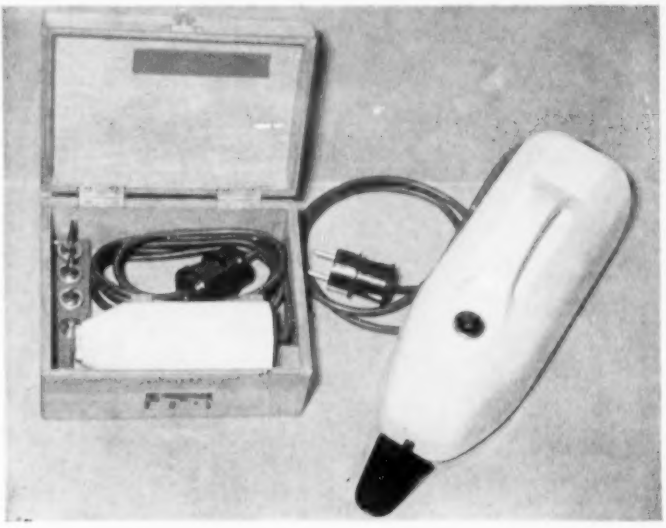

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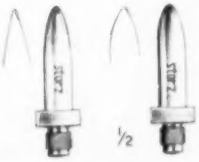

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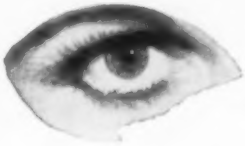

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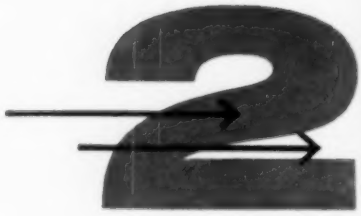

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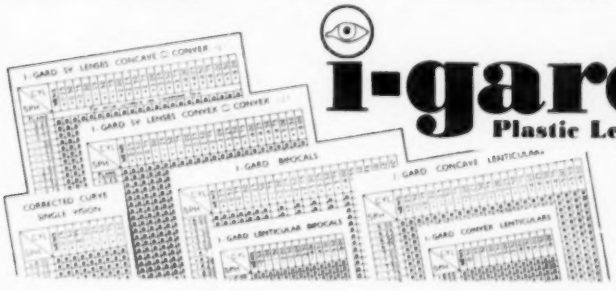

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  for children in grades 4, 5, and 6
- FINDING YOURSELF
  for boys and girls of approximately junior high school age
- LEARNING ABOUT LOVE
  for young people of both sexes (about 16 to 20 years of age)
- FACTS AREN'T ENOUGH
  for adults who have any responsibility for children or youth that may create a need for an understanding of sex education

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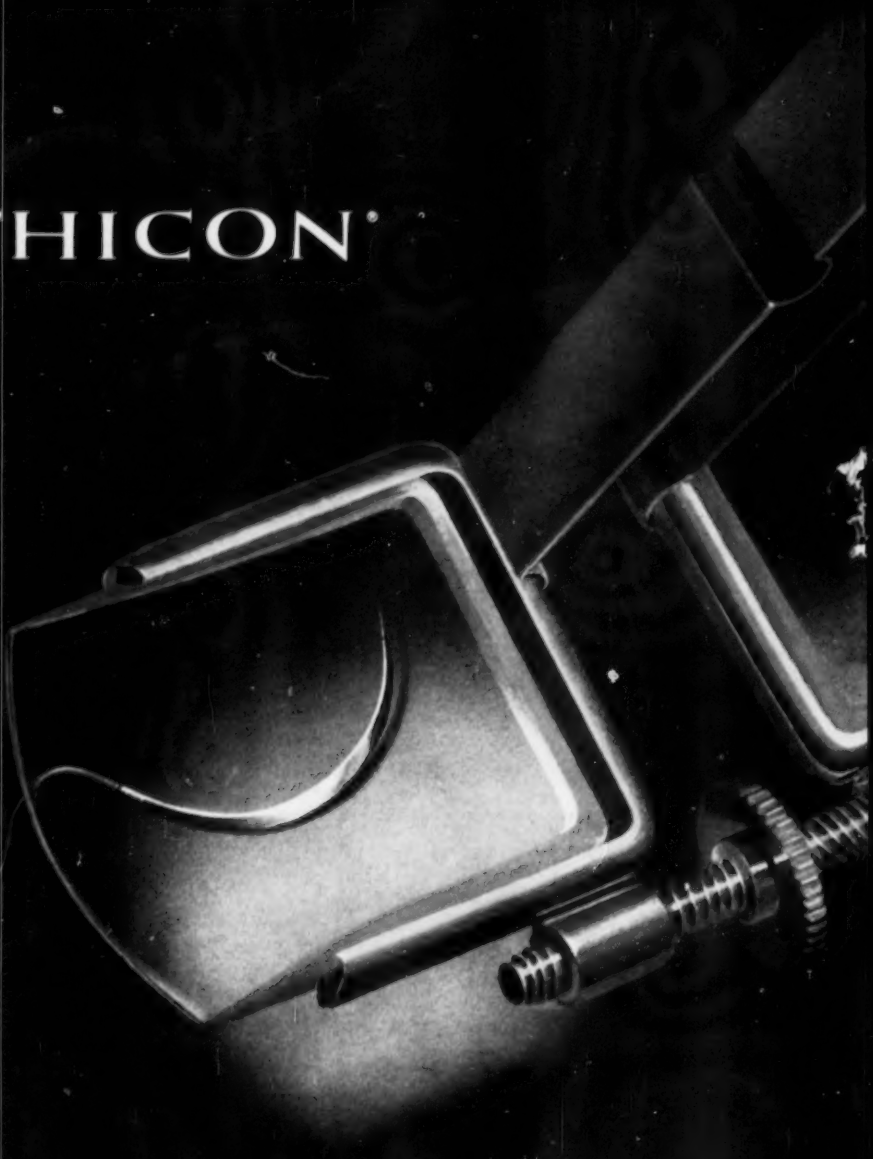

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